APPENDIX A — OPINION OF THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT DECIDED DECEMBER 26, 2006

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

05-1396, -1429, -1430

ELI LILLY AND COMPANY and
LILLY INDUSTRIES LIMITED,

Plaintiffs-Appellees,

v.

ZENITH GOLDLINE PHARMACEUTICALS, INC.
(now known as Ivax Pharmaceuticals, Inc.),

Defendant-Appellant,

and

TEVA PHARMACEUTICALS USA, INC.,

Defendant-Appellant,

and

DR. REDDY'S LABORATORIES, LTD.,

Defendant-Appellant.

DECIDED: December 26, 2006

Appendix A

Before RADER, SCHALL, and GAJARSA, *Circuit Judges.*

RADER, *Circuit Judge.*

Zenith Goldline Pharmaceuticals, Inc. (now known as IVAX Pharmaceuticals, Inc.) (IVAX); Dr. Reddy's Laboratories, Ltd. (DRL); and Teva Pharmaceuticals USA, Inc. (Teva) (defendants), filed an Abbreviated New Drug Application (ANDA). In response, the plaintiffs, Eli Lilly and Company and Lilly Industries Ltd. (collectively Lilly), filed suit against all defendants for infringement of United States Patent No. 5,229,382 ('382 patent). Following a two and one-half week bench trial, the United States District Court for the Southern District of Indiana found the '382 patent valid and infringed. *Eli Lilly & Co. v. Zenith Goldline Pharm.*, 364 F.Supp.2d 820 (S.D.Ind.2005) *(Final Judgment); Eli Lilly & Co. v. Zenith Goldline Pharm.*, 1:01-cv-443-RLY-VSS (S.D.Ind. May 9, 2005) (*Amended Final Judgment*). In 221 pages of written analysis, the trial court documented its findings and conclusions. *Eli Lilly & Co. v. Zenith Goldline Pharm.*, 364 F.Supp.2d 820 (S.D.Ind.2005) (*Findings of Fact and Conclusions of Law*). The defendants appeal the trial court's conclusions on the validity of the '382 patent and inequitable conduct. Finding no reversible error, this court affirms.

I.

The '382 patent claims both olanzapine and use of the compound to treat schizophrenia. *Findings of Fact and Conclusions of Law*, 364 F.Supp.2d at 830. A Lilly research chemist first synthesized olanzapine in the United Kingdom

in 1982. *Id.* at 834. Lilly filed the '382 patent application on May 22, 1992. The patent issued on July 20, 1993. The United States Food and Drug Administration (FDA) approved olanzapine, sold by Lilly under the trademark Zyprexa®, in late 1996. *Findings of Fact and Conclusions of Law*, 364 F.Supp.2d at 830. By filing an ANDA, the defendants stipulate to infringement if the '382 patent is valid and enforceable. *Amended Final Judgment,* slip op. at 1.

Claims 1, 2, 3, 7, 8, and 15 of the '382 patent set forth the boundaries of the invention:

> 1. 2-Methyl-10-(4-methyl-1-piperazinyl)-4H-thieno[2,3-b][1,5]benzodiazepine, or an acid addition salt thereof.
>
> 2. A pharmaceutical composition comprising a compound according to claim 1 or a pharmaceutically acceptable acid addition salt thereof together with a pharmaceutically acceptable diluent or carrier therefor.
>
> 3. A pharmaceutical composition in capsule or tablet form comprising from 2.5 to 5 mg of the compound of claim 1 together with a pharmaceutically acceptable diluent or carrier therefor.
>
> * * * *
>
> 7. A method of claim 5 for treating an animal, including a human, suffering from or susceptible to schizophrenia.

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8. A method of claim 7 wherein the effective amount is from 0.1 to 20 mg per day of 2-methyl-10-(4-methyl-1-piperazinyl)-4H-thieno[2,3-b][1,5]benzodiazepine, or a pharmaceutically acceptable acid addition solution salt thereof.

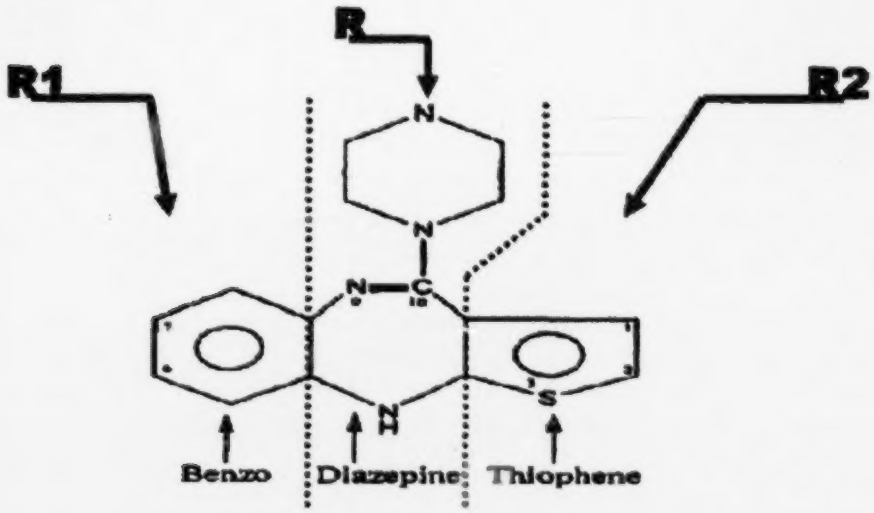
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15. A pharmaceutical composition in capsule or tablet form comprising from 0.1 to 20 mg of the compound of claim 1 together with a pharmaceutically acceptable diluent or carrier therefor.

'382 patent, col. 12, ll. 10-20, ll. 33-40, ll. 64-67.

Before discovery of olanzapine, Lilly discovered other drugs in the same family of compounds (thienobenzodiazepines), namely clozapine, flumezapine, ethyl flumezapine and ethyl olanzapine (a.k.a. Compound '222). *Findings of Fact and Conclusions of Law*, 364 F.Supp.2d at 831-33. These compounds share a common

structural nucleus as thienobenzodiazepines, namely a piperazine ring (R), a benzene ring (R1), and a thiophene ring (R2).



Lilly used clozapine to treat some forms of schizophrenia in the late '60s and early '70s. *Findings of Fact and Conclusions of Law*, 364 F.Supp.2d at 831. Clozapine was thus the first "atypical" antipsychotic drug. Structurally, olanzapine differs from clozapine in that olanzapine has a methyl-substituted thiophene ring in place of the benzene ring in clozapine. *Id.* at 846-47. Olanzapine also has hydrogen in place of the chlorine on its benzene ring. *Id.* at 847.

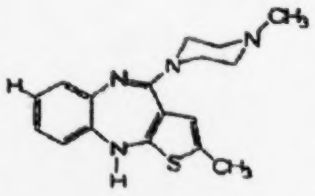
Despite its advantages, researchers discovered in 1975 that clozapine caused an often fatal blood disorder (agranulocytosis) in one percent of patients. For that reason, Lilly withdrew clozapine from the market. *Id.* Nevertheless, after a general failure to replace clozapine, reflected by many

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documented reports of promising compounds that failed either for lack of efficacy or toxic side-effects, the FDA, in late 1989, approved clozapine with careful blood-monitoring. *Id.* at 832.

Until discovery of olanzapine, researchers attributed the efficacy of clozapine and typical antipsychotics to their "neuroleptic substituent"-an electron-withdrawing group considered important to the antipsychotic activity of the compounds. *Id.* Halogen-a fluorine (F) or chlorine (Cl) atom-is such an electron withdrawing group. *Id.* at 832, 850.

Olanzapine does not have a halogen atom, i.e. a fluorine (F) or chlorine (Cl) atom. Instead, it has a hydrogen atom (H), which is not an electron withdrawing (or electronegative) group. *Id.* at 850.

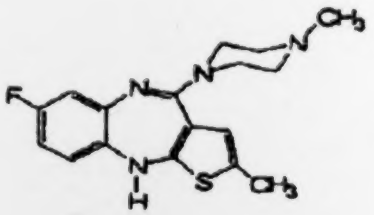


Olanzapine

The prior art to olanzapine includes ethyl flumezapine and flumezapine, both disclosed in U.S. Patent No. 4,115,574 ('574 patent) that issued in 1978. The prior art also includes ethyl olanzapine (a.k.a. Compound '222). Ethyl flumezapine caused widespread blood problems in dogs. *Id.* at 847. Flumezapine caused extra-pyramidal symptoms (EPS) and an increase in liver enzymes and a muscle enzyme called creatine phosphokinase (CPK). Ethyl olanzapine caused a

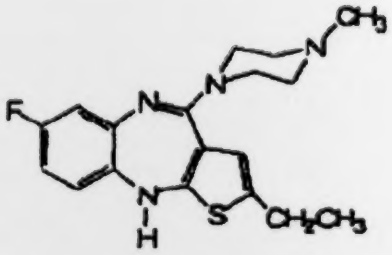
significant increase in cholesterol in female beagle dogs. *Id.* Thus, the prior art to olanzapine had significant detrimental side effects.

Olanzapine differs structurally from flumezapine, by substitution of a hydrogen atom (H) for the fluorine atom (F) in flumezapine at the 7-position of the benzene ring. *Id.*



Flumezapine

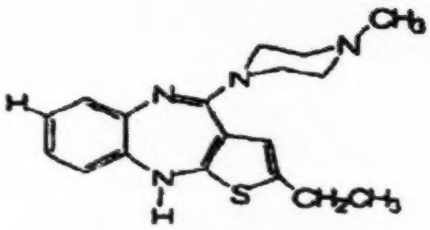
Olanzapine differs structurally from ethyl flumezapine by replacement of the fluorine atom (F) and ethyl group (CH_2CH_3) in ethyl flumezapine with a hydrogen atom (H) and methyl group (CH_3) respectively. *Id.*



Ethyl Flumezapine

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Olanzapine differs structurally from its ethyl analog, Compound '222 (ethyl olanzapine), by replacement of the ethyl group (CH_2CH_3) with a methyl group (CH_3) at the 2-position of the thiophene ring. *Id.*



Ethyl Olanzapine (Compound '222)

I

The trial court found that the defendants did not prove by clear and convincing evidence that claims 1, 2, 3, 7, 8, and 15 of the '382 patent were invalid as anticipated under 35 U.S.C. § 102. *Findings of Fact and Conclusions of Law*, 364 F.Supp.2d at 922-23. The primary reference the defendants cited for anticipation of these claims is an article entitled "4-Piperazinyl-10*H*-thieno[2,3-*b*][1,5] benzodiazepines as Potential Neuroleptics" from the Journal of Medicinal Chemistry in 1980 (*Chakrabarti 1980a*). Jiban K. Chakrabarti, Linda Horsman, et al., *4-Piperazinyl-10H-thieno[2,3-b] [1,5]benzodiazepines as Potential Neuroleptics,* 23 J. Med. Chem. 8 (1980).

Anticipation is a question of fact, including whether or not an element is inherent in the prior art. *See In re Schreiber,* 128 F.3d 1473, 1477 (Fed.Cir.1997). Therefore, this court reviews a finding of anticipation under the clearly erroneous standard. *Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1346 (Fed.Cir.1999). To anticipate, a prior art reference must

place the inventive compound or composition in the possession of the public. *In re Brown,* 51 C.C.P.A. 1254, 329 F.2d 1006, 1011 (1964). Thus, the prior art reference must disclose each and every feature of the claimed invention, either explicitly or inherently. *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047 (Fed.Cir.1995).

Pointing to *In re Petering,* 49 C.C.P.A. 993, 301 F.2d 676 (1962) and *In re Schaumann,* 572 F.2d 312 (C.C.P.A.1987), IVAX asserts that *Chakrabarti 1980a* anticipated claim 1 of the 2382 patent because it identified compounds from the same family of compounds (thienobenzodiazepines). Indeed, in *Petering,* the Board of Patent Appeals affirmed the examiner's rejection of claims 1, 2, 4, 5, 7, and 10-12 of the patent applicant's application on "isoalloxazines." 301 F.2d at 677. However, in contrast to this case, the prior art in *Petering* did more than make a broad generic disclosure. In *Petering,* the prior art disclosed a limited number of specific preferences from a specifically defined group of isoalloxazines. *Id.* As a result, *Petering* actually disclosed to one skilled in the art a limited class of only "some 20 compounds," including "6, 7-dimethyl-9-(Bmonohydroxyethyl)-isoalloxazine." *Schaumann,* 572 F.2d at 315 (citing *Petering,* 301 F.2d at 682).

Similarly, the prior art in *Schaumann* disclosed 14 compounds, later further narrowed to 7, considering express preferences. Additionally, the structural formula of this prior art contained but a single variable. 572 F.2d at 314. Thus, in *Schaumann,* the prior art patent embraced a very limited number of closely related compounds and specifically described the claimed compound. 572 F.2d at 316. Thus,

unlike this case, the prior art in both *Petering* and *Schaumann* expressly spelled out a definite and limited class of compounds that enabled a person of ordinary skill in the art to at once envisage each member of this limited class. *Schaumann,* 572 F.2d at 315; *Petering,* 301 F.2d at 681-82.

By contrast, the number of compounds actually disclosed by *Chakrabarti 1980a* numbers in the millions (including all proposed alternative substituents). *Chakrabarti 1980a* examined forty-five specific compounds (as opposed to a genus of compounds) in the 4-piperazinyl-10H-thieno [2,3-b] [1,5]benzodiazepine family and fourteen analogous 5-piperazinyl-substituted 4H-thieno[2,3-b][1,4] benzodiazepines, which were created to compare activity. *Findings of Fact and Conclusions of Law,* 364 F.Supp.2d at 848. Indeed, *Chakrabarti 1980a* listed several preferred compounds and substituents, none of which resemble olanzapine:

> for R-a methyl, hydroxyethyl, or hydroxypropyl;
>
> for R1-a fluorine, chlorine, or 7, 8, di-fluoro *[no hydrogen];* and
>
> for R2-a methyl, 2-ethyl, or 2-isopropyl group.

Id. at 848. Five of the preferred individual compounds (9, 12, 17, 29, and 34) are more potent than clozapine (scoring a 3 CAR [1] or higher) and have clozapine-like effect. For those

1. Conditioned Avoidance Response (CAR): The CAR test evaluates the inhibition of a behavioral response in rats. The CAR (Cont'd)

five preferred compounds, the *Chakrabarti 1980a* authors expressed a preference for specific, complete compounds without any variation of the individual substituents on those molecules. *Chakrabarti 1980a* also always expressed a preference for halogen-containing compounds (fluorine or chlorine), not hydrogen. *Id.* at 832-33. Furthermore, compounds 9, 12, 17, and 29 all have fluorine at the 7-position of the benzene ring. And though Compound 34 does have hydrogen at the 7-position of the benzene ring, it has a hydroxyethyl on its piperazine ring, unlike olanzapine. *Id.* In sum, *Chakrabarti 1980a* discloses nothing close to the claimed invention.

Chakrabarti 1980a does provide a general structural formula with possible substituents of "R," "R1," and "R2," but it does not define them at all. *Findings of Fact and Conclusions of Law*, 364 F.Supp.2d at 900. No possible combination of those preferred substituents would lead to the components that make up olanzapine, because each would contain a fluorine or a chlorine. To make olanzapine from *Chakrabarti 1980a*, one would have to depart from the teaching of the article and recombine the components of the specific illustrative compounds with hindsight. Thus, *Chakrabarti 1980a* does not anticipate because: (1) the article prefers complete compounds, not individual substituents, (2) the article discloses no generic disclosure encompassing olanzapine or even stating that substituents on different compounds were interchangeable, and (3) the article does

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(Cont'd)
test was the only measure of potential antipsychotic activity, and if the compound did not achieve a CAR score of three or four at a dose of less than 30 mg/kg, it was not considered active.

not suggest transforming unpreferred compound 7[2] into a preferred compound. Thus, *Chakrabarti 1980a* did not place olanzapine in the possession of the public. Therefore, this court detects no clear error in the trial court's finding of no anticipation.

II

The trial court found that the defendants did not prove by clear and convincing evidence that claims 1, 2, 3, 7, 8, and 15 of the '382 patent were invalid as obvious under 35 U.S.C. § 103. *Findings of Fact and Conclusions of Law*, 364 F.Supp.2d at 922-23. On appeal, IVAX argues that the district court erred by erecting "a threshold requirement that defendants establish a teaching or incentive to treat the closest prior art (i.e., Compound '222) as a 'lead compound.'" IVAX also charges that the district court disregarded (1) the structural characteristic of olanzapine as the adjacent homolog of Compound '222, (2) the suggestions to delete fluorine from the prior art compound flumezapine, and (3) the observation that Compound '222 and flumezapine "bracket" olanzapine.

This court reviews obviousness without deference as a legal conclusion with underlying factual determinations which are reviewed for clear error. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1164 (Fed.Cir.2006). The factual underpinnings are: (1) the scope and content of the prior art,

2. Furthermore, compound 7 (like compound '222) lacks the electron withdrawing "neuroleptic substituent" believed at that time to be necessary for antipsychotic efficacy.

(2) the differences between the prior art and the claimed invention at the time of invention, (3) the level of ordinary skill in the art, and (4) the objective indicia of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966); *Panduit Corp. v. Dennison Mfg.*, 810 F.2d 1561, 1566-67 (Fed.Cir.1987). For a chemical compound, a prima facie case of obviousness requires "structural similarity between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed compositions." *In re Dillon*, 919 F.2d 688, 692 (Fed.Cir.1990) (en banc). "[A] reasonable expectation of success, not absolute predictability" supports a conclusion of obviousness. *In re Longi*, 759 F.2d 887, 896 (Fed.Cir.1985).

For the following reasons, the district court did not err in reaching its conclusion. As succinctly stated by the district court:

> 175. In light of the general state of the art, including the teachings of the '574 patent and *Chakrabarti 1980a*, *Chakrabarti 1982*, and *Chakrabarti 1989*, one of ordinary skill in the art would have expected that replacing the fluorine atom with a hydrogen atom would produce a compound without sufficient antipsychotic activity. Nichols Tr. 2776:5-11.
>
> 176. While *Chakrabarti 1980a* suggests that a chlorine atom in place of the fluorine atom would also enhance the compound's activity, it *does not specifically suggest that the same result*

> *could be obtained with a hydrogen atom.* Nichols Tr. 2779: 17-24; TX 3465 at 879, col. 2. Nor does anything in *Sullivan and Franklin* suggest the desirability of using a hydrogen atom at this position. Nichols 2776:5-11; TX 3161; Findings of Fact § IV. B.1.d. *If one were looking to replace the fluorine, one would replace the fluorine with other electronegative groups, not hydrogen.* TX 1315 at 3172; LaVoie Tr. 1572:12-1573:18. Indeed, the art as a whole teaches directly away from using hydrogen because it is not an electron-withdrawing substituent.

Findings of Fact and Conclusions of Law, 364 F.Supp.2d at 850 (emphases added). Though the '574 patent disclosed Compound '222, the patent expressed *a preference* for halogen containing compounds and specifically those with a halogenated substituent on the benzene ring in a location analogous to the chlorine in clozapine. *Findings of Fact and Conclusions of Law*, 364 F.Supp.2d at 845. These teachings do not suggest or make obvious, among other things, olanzapine's hydrogen component. The prior art references at the time of this invention taught away from using a non-halogenated compound as a substituent in the benzene ring, exactly where olanzapine has a hydrogen atom.

Furthermore, the trial court found that a person of ordinary skill in the art would not have chosen Compound '222 as the beginning compound because it contained a hydrogen atom instead of a halogen atom, which again is not a preferred substituent. *Findings of Fact and Conclusions of Law*, 364 F.Supp.2d at 849-50. In addition, the prior art

supplied no motivation to change the 2-ethyl in Compound '222 to a 2-methyl. The prior art would have instead suggested modification by adding a halogen atom to supply the neuroleptic substituent as a trigger for antipsychotic activity. *Id.* The district court found that, at the relevant time, a person with ordinary skill in the art would not have expected any reasonable chance of success with other clozapine-like compounds. *Id.* at 850-52.

And though olanzapine is also the adjacent homolog of Compound '222, patentability for a chemical compound does not depend only on structural similarity. *Comm'r of Patents v. Deutsche Gold-und-Silber-Scheideanstalt Vormals Roessler,* 397 F.2d 656 (D.C.Cir.1968). This court will not ignore a relevant property of a compound in the obviousness calculus. *In re Lalu,* 747 F.2d 703 (Fed.Cir.1984). When claimed properties differ from the prior art, those differences, if unexpected and significant, may lead to nonobviousness. *In re Mehta,* 52 C.C.P.A. 1615, 347 F.2d 859 (1965); *In re Grabiak,* 769 F.2d 729 (Fed.Cir.1985). In this case, the trial court noted some structural similarity of olanzapine and the prior art, but also accounted for the unexpected beneficial properties in olanzapine.

This case is similar in many respects to *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.,* 231 F.3d 1339, 1344 (Fed.Cir.2000). In *Yamanouchi,* this court held that the ANDA filer did not show obviousness of the famotidine compound:

> [The ANDA filer] did not show sufficient motivation for one of ordinary skill in the art at

> the time of invention to take any one of the following steps, let alone the entire complex combination: (1) selecting example 44 as a lead compound, (2) combining the polar tail from example 44 with the substituted heterocycle from tiotidine, and (3) substituting the carbamoyl (CONH2) group in the intermediate compound with a sulfamoyl group (SO2NH2) to create famotidine.

Id. Likewise, in this case, the defendants have not shown that a person ordinarily skilled in this art would have selected Compound '222 as a lead compound because it contained hydrogen rather than fluorine or chlorine. At the time of invention, the state of the art would have directed the person of ordinary skill in the art away from unfluorinated compounds like Compound '222. After all, the primary example of the state of the art at that time, the '574 patent, did not provide any biological data for compound '222, suggested a preference for halogen-containing compounds, and identified a fluorine-containing compound, ethyl flumezapine, as "particularly active." *Findings of Fact and Conclusions of Law*, 364 F.Supp.2d at 904. Moreover, as the trial court detailed, *Chakrabarti 1980a* expressly taught that the addition of a fluorine or chlorine enhanced anti-psychotic activity. It also taught that the unfluorinated Compound '222 was less active than the benchmark compound, clozapine. *Id.* Thus, rather than providing the requisite motivation, the prior art taught away from selecting Compound '222 as a lead compound for further development.

Nevertheless, citing to an article entitled "*In Vitro* Thiomethylation: Studies with Flumezapine," written by H.R. Sullivan and R.B. Franklin (S & F article), IVAX argues that removal of fluorine from flumezapine would have resulted in a default to a hydrogen atom. H.R. Sullivan and R.B. Franklin, *In Vitro Thiomethylation: Studies with Flumezapine*, 13 Drug & Metabolism Disposition 276 (1985). To the contrary, however, the *S & F* article says nothing whatsoever about removal of fluorine. Specifically, the article discusses the metabolism of flumezapine in dogs that produces methylthio metabolite. *Id.* The *S & F* article does not state that flumezapine is toxic or that the methylthio metabolite could be avoided by replacement of fluorine with hydrogen. As noted by the district court, the *S & F* article "does not teach that replacing the fluorine with a hydrogen atom would stop the formation of the methylthio metabolite. Indeed, acetaminophen (Tylenol ®), a non-fluorinated compound, also forms methylthio metabolite." *Findings of Fact and Conclusions of Law*, 364 F.Supp.2d at 846-47. The trial court correctly concluded that nothing in the *S & F* article suggested "that a hydrogen atom in place of the fluorine atom . . . would be desirable . . . or that to make such a substitution would avoid the formation of the methylthio metabolite." *Id.*

Beyond the nonobvious selection step, the prior art also did not suggest any of the other modifications necessary to reach olanzapine. Thus, even if the *S & F* article taught what IVAX claims, the skilled artisan would still need to combine those teachings with compound 34 in *Chakrabarti 1980a* to reach olanzapine. As taught by *Yamanouchi Pharm. Co.* and other precedent, mere identification in the prior art of each

component of a composition does not show that the combination as a whole lacks the necessary attributes for patentability, i.e. is obvious. *In re Kahn*, 441 F.3d 977, 986 (Fed.Cir.2006) (citing *In re Rouffet*, 149 F.3d 1350, 1355 (Fed.Cir.1998)). Rather, to establish a prima facie case of obviousness based on a combination of elements in the prior art, the law requires a motivation to select the references and to combine them in the particular claimed manner to reach the claimed invention. *Id.* In conclusion, because flumezapine caused EPS in two patients, elevations in CPK and a variety of liver enzymes in a number of patients, substantial evidence supports the trial court's conclusion that the S & F article would not have led a person of ordinary skill in the art to believe that flumezapine could be successfully modified with a hydrogen atom. The district court correctly concluded that nothing in the S & F article and *Chakrabarti 1980a* made the combination reached in olanzapine obvious.

Nonetheless, IVAX also cites to *In re Payne*, 606 F.2d 303 (C.C.P.A 1979) to argue that Compound '222 and flumezapine "bracket," and thereby make olanzapine prima facie obvious. To the contrary, *Payne* did not feature prior art that taught away from making the structural alterations as in this case. In this case, the prior art would have directed one of skill away from making flumezapine and ethyl-olanzapine (Compound '222). The "bracket" notion from *Payne* simply characterized the structural similarity in that case, which this court has noted does not control this case.

Furthermore, Lilly overcame any prima facie case of obviousness. Among other things, Lilly proved extensive

secondary considerations to rebut obviousness. The trial court found the evidence clearly established four of the five proffered secondary considerations. *Findings of Fact and Conclusions of Law*, 364 F.Supp.2d at 852-74, 905-12. Lilly established (1) a long-felt and unmet need; (2) failure of others; (3) industry acclaim; and (4) unexpected results. *Id.* The record shows a long-felt need for a safer, less toxic, and more effective clozapine-like drug; a decade (or more) of failure to find a replacement for clozapine; a reasonable amount of commercial success for olanzapine; and a number of awards for olanzapine as indicators of industry acclaim. *Id.* at 852-53. Specifically, the trial court noted a "long-felt but unsolved need for a safe atypical antipsychotic from 1975 until 1990," as well as extensive evidence supporting the other objective criteria. *Id.* at 832-34, 906. The trial court also discussed the unexpected differences between the closest analog, Compound '222 and olanzapine, most of which focused on olanzapine not raising cholesterol levels in dogs, and a comparison of some humans tests with other similar drugs that raised CPK. *Id.* at 853-73. In sum, these objective criteria buttressed the trial court's conclusion of nonobviousness.

III

The trial court concluded that Lilly's clinical trials of olanzapine were not a public, but an experimental, use that negated any section 102 bar. *Findings of Fact and Conclusions of Law*, 364 F.Supp.2d at 913-14. Under section 102, a person is entitled to a patent, unless "the invention was . . . in public use . . . in this country, more than one year prior to the date of the application for patent in the United

States." 35 U.S.C. § 102(b) (2000). Public use includes "any [public] use of [the claimed] invention by a person other than the inventor who is under no limitation, restriction or obligation of secrecy to the inventor." *In re Smith*, 714 F.2d 1127, 1134 (Fed.Cir.1983) (citing *Egbert v. Lippmann*, 104 U.S. 333, 336, 26 L.Ed. 755 (1881)).

In considering whether a particular use was "public" within the meaning of section 102(b), this court considers the policies underlying the bar. *Tone Bros., Inc. v. Sysco Corp.*, 28 F.3d 1192, 1198 (Fed.Cir.1994), *cert. denied*, 514 U.S. 1015, 115 S.Ct. 1356, 131 L.Ed.2d 214 (1995). In assessing this case, the trial court found that Lilly personnel conducted the HGAA, HGAB, and HGAC Phase I clinical trials of olanzapine in the Lilly clinic. *Findings of Fact and Conclusions of Law*, 364 F.Supp.2d at 912-13. In all three stages, Lilly restricted access to the facility and provided full-time security. *Id.* Lilly closely monitored and confined the movements of the volunteers, who were healthy and not suffering from schizophrenia, for the duration of the study. *Id.* Visitors to the volunteers did not interrupt the control or confidentiality of the study. *Id.* Moreover, as the trial court noted, the clinical trials did not use the drugs to treat schizophrenic patients, but merely to test the safety and efficacy of the drug. *Findings of Fact and Conclusions of Law*, 364 F.Supp.2d at 913.

Beyond this convincing record evidence, the experimental character of these tests negated any statutory bar. Even a use that occurs in the open may not invoke a bar when undertaken to experiment on or with the claimed invention. *TP Labs., Inc. v. Prof'l Positioners, Inc.*, 724 F.2d

965, 971 (Fed.Cir.1984), *cert. denied*, 469 U.S. 826, 105 S.Ct. 108, 83 L.Ed.2d 51 (1984). In the words of the Supreme Court, "[t]he use of an invention by the inventor himself, or of any other person under his direction, by way of experiment, and in order to bring the invention to perfection, has never been regarded as [a public] use." *City of Elizabeth v. Am. Nicholson Pavement Co.*, 97 U.S. 126, 134, 24 L.Ed. 1000 (1877). Several indicia may show the negating experimental character of a use, including (1) the length of the test period, (2) any confidentiality agreement, (3) any records of testing, (4) any monitoring and control of the test results, (5) the number of tests, and (6) the length of the test period in relation to tests of similar inventions. *TP Labs.*, 724 F.2d at 971-72; *see also In re Brigance*, 792 F.2d 1103, 1108 (Fed.Cir.1986). In this case, Lilly tailored its tests to their experimental drug safety and efficacy purpose, adequately monitored for results, and maintained confidentiality throughout the duration of the study. The trial court did not err in finding no public use.

IV

DRL argues that the district court erred in not finding inequitable conduct because if it had looked at the totality of the circumstances, the evidence would have shown that Lilly intentionally made *per se* material statements that misled the examiner. "Inequitable conduct occurs when a patentee breaches his or her duty to the United States Patent and Trademark Office (PTO) of 'candor, good faith, and honesty.' " *Warner-Lambert Co. v. Teva Pharms. USA, Inc.*, 418 F.3d 1326, 1342 (Fed.Cir.2005) (quoting *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1178 (Fed.Cir.1995)). Inequitable conduct includes affirmative misrepresentations of material

facts, non-disclosure of material information, or submission of false material information, coupled with an intent to deceive. *See Nobelpharma AB v. Implant Innovations, Inc.*, 141 F.3d 1059, 1068-71 (Fed.Cir.1998) (citing *Molins*, 48 F.3d at 1178). To assess inequitable conduct, the trial court must determine whether the withheld reference meets a threshold level of materiality. *Dayco Prods., Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1362-63 (Fed.Cir.2003) (quoting *Purdue Pharma L.P. v. Boehringer Ingelheim GMBH*, 237 F.3d 1359, 1366 (Fed.Cir.2001)). Then, the trial court must also determine whether the evidence shows a threshold level of intent to mislead the PTO. *See Halliburton Co. v. Schlumberger Tech. Corp.*, 925 F.2d 1435, 1439 (Fed.Cir.1991). After finding the threshold levels of materiality and intent, the trial court then balances those factors. *See Molins*, 48 F.3d at 1178.

Gross negligence alone is insufficient to justify an inference of intent to deceive the PTO. *See Kingsdown Med. Consultants, Ltd. v. Hollister, Inc.*, 863 F.2d 867, 876 (Fed.Cir.1988); *FMC Corp. v. Manitowoc Co.*, 835 F.2d 1411, 1415 n. 9 (Fed.Cir.1987). In a case involving an omission of a material reference to the PTO, the record must contain clear and convincing evidence that the applicant made a deliberate decision to withhold a known material reference. *See Molins*, 48 F.3d at 1181. Beyond that, the applicant must have withheld the material subject matter with the intent to deceive. *Ferring B.V. v. Barr Labs., Inc.*, 437 F.3d 1181, 1190 (Fed.Cir.2006). "Intent to deceive cannot be inferred simply from the decision to withhold the reference where the reasons given for the withholding are plausible." *Dayco Prods.*, 329 F.3d at 1368.

Appendix A

Before the Swedish Board, Lilly noted idiosyncratic blood toxicity problems in isolated dogs at 10 mg/kg, and DRL claims Lilly's failure to mention this to the PTO is inequitable conduct. However, the PTO had questions only about blood cholesterol levels. Before the Swedish Board, Lilly never commented about cholesterol levels. Indeed, Lilly's statements to the Swedish Board about the idiosyncratic blood toxicity resulted from Lilly's desire to conduct human clinical studies of olanzapine in Scandinavia. *Findings of Fact and Conclusions of Law*, 364 F.Supp.2d at 875-76. Before allowing human clinical studies, the Swedish Board required Lilly to respond to concerns about the toxic effects of olanzapine on blood cells and bone marrow in dogs during the D07290 Dog Study. *Id.* at 919-20. Lilly replied that these findings of hematoxicity "were believed not to have clinical relevance to humans since the effects occurred at large multiples of the clinical dose." *Id.* at 875-76. These statements to the Swedish Board discounted the results of the blood studies by reference to idiosyncratic hematoxicity, not cholesterol problems. Thus, Lilly did not fail to disclose information or contradict its later patentability arguments.

Furthermore, contrary to DRL's argument, Dr. David Scruby's declaration did not create a "false" impression that the D07290 Dog Study cholesterol findings could be extrapolated to humans. Dr. Scruby had been a staff physician at Lilly since 1983. *Findings of Fact and Conclusions of Law*, 364 F.Supp.2d at 882. This court acknowledges that *Rohm & Haas, Co. v. Crystal Chem. Co.*, 722 F.2d 1556, 1571 (Fed.Cir.1983) states: "[T]here is no room to argue that submission of false affidavits is not material." In this case,

however, the record shows that Dr. Scruby's affidavit was not false.

Dr. Scruby's affidavit could only be considered false if read to suggest that Dr. Scruby was telling the examiner to extrapolate point-by-point to humans olanzapine's improved cholesterol levels in dogs as compared to Compound '222. Dr. Scruby's affidavit does not suggest such an extrapolation of the benefits of olanzapine from dogs to humans. Dr. Scruby, in fact, separates into different paragraphs his discussions of olanzapine's benefits for cholesterol levels in humans and the effects of Compound '222 for dogs. Furthermore, he expressly relies on the declarations of Dr. Jeffrey Means and Dr. James Symanowski as "the basis for my clinical statements concerning the dog toxicology studies." Dr. Means is a pharmacologist and toxicologist; and Dr. Symanowski is a statistician. *Findings of Fact and Conclusions of Law*, 364 F.Supp.2d at 837-38.

Dr. Scruby's affidavit appears in the prosecution history as a Response After Final (*Response*) for the following propositions: (1) that "cholesterol is recognized as a factor in coronary artery disease;" (2) that the Framingham Study "indicated that a 1% reduction in the cholesterol level results in a 2% reduction in coronary artery disease;" and (3) that "there is overwhelming evidence in the literature that serum cholesterol in excess of 240 mg/dL is a significant contributor to the genesis of atherosclerosis." These statements are not false. The trial court did not err in discerning no clear and convincing evidence that Dr. Scruby misrepresented or withheld information from the PTO with an intent to deceive. *Id.* at 883-84.

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Lilly's *Response* did not intentionally blur the distinctions between humans and dogs. Rather, Lilly's *Response* expressly replied to the examiner's request for human clinical comparisons of olanzapine and Compound '222 by stating:

> Applicants maintain that the Examiner's *request for human clinical comparison of olanzapine and compound '222 is inappropriate* . . . . In light of serious consequences associated with artificially altering the balance of cholesterol synthesis, Applicants *assert that human clinical trials with '222 would be unethical and well as unreasonable.*

Response, at p. 11 (emphases added). Lilly made clear that it based none of its statements about the effects of either olanzapine or Compound '222 on human testing. Furthermore, the examiner also understood that the cholesterol data was based on the D07290 Dog Study because he asked about those results without any reference to cholesterol benefits for humans. *Findings of Fact and Conclusions of Law*, 364 F.Supp.2d at 882.

In addition, on a separate inequitable conduct question, the trial court concluded that Lilly did not omit material subject matter from its Information Disclosure Statement in April 1991, which did not disclose the '574 patent and *Chakrabarti 1980a. Id.* at 917. The trial court also found no clear and convincing evidence that Lilly withheld *Chakrabarti 1980a* or the '574 patent with an intent to deceive the PTO. *Id.* at 917. The trial court noted that Lilly

did disclose U.S. Patent No. 4,115,568 ('568 patent) to the PTO, and specifically explained that "[t]he reference fails to disclose the compound which is now claimed, but does describe the adjacent homologue [Compound '222]." *Id.* at 894. It also noted that the technical disclosures of the '574 and '568 patents are identical and each discloses the genus of compounds that generically includes olanzapine. Moreover, Lilly cited the British counterpart of the '574 and '568 patents in the olanzapine patent application. In addition, the examiner found and relied on *Chakrabarti 1980a* during prosecution. As a result, the trial court did not err in its conclusion that nondisclosure of *Chakrabarti 1980a* or the '574 patent was neither a material omission nor done with an intent to deceive.

V

In conclusion, this court affirms the trial court on anticipation, obviousness, and public use questions. Because the parties do not dispute the facts, this court also affirms the trial court's legal conclusions on inequitable conduct finding no abuse of discretion therein.

COSTS

Each party shall bear its own costs.

AFFIRMED.

APPENDIX B — FINDINGS OF FACT AND CONCLUSIONS OF LAW OF THE UNITED STATES DISTRICT COURT FOR THE SOUTHERN DISTRICT OF INDIANA, INDIANAPOLIS DIVISION DATED APRIL 14, 2005

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF INDIANA
INDIANAPOLIS DIVISION

1:01-cv-443-RLY-VSS

ELI LILLY AND COMPANY and
LILLY INDUSTRIES LTD.,

Plaintiffs,

vs.

ZENITH GOLDLINE PHARMACEUTICALS, INC.,
DR. REDDY'S LABORATORIES, LTD., and
TEVA PHARMACEUTICALS USA, INC.,

Defendants.

FINDINGS OF FACT AND CONCLUSIONS OF LAW

[Table of Contents intentionally omitted]

Plaintiffs, Eli Lilly and Company and Lilly Industries Ltd., filed suit against the Defendants, Zenith Goldline Pharmaceuticals, Inc., Dr. Reddy's Laboratories, Ltd., and Teva Pharmaceuticals USA, Inc. (collectively "Defendants"), for infringement of United States Patent No. 5,229,382 ("'382 patent"). The parties tried this case before the court from

January 26, 2004, through February 12, 2004. Following the trial, the parties filed proposed findings of fact and conclusions of law, and responses thereto. The parties also filed post-trial briefs, which the court found helpful given the breadth and complexity of the disputed issues. The majority of the relevant briefing was submitted by May 12, 2004, with final submissions filed in February 2005.

Being duly advised, the court finds that Defendants have failed to prove by clear and convincing evidence that the '382 patent is invalid, as anticipated under 35 U.S.C. § 102, as obvious under 35 U.S.C. § 103, under the doctrine of double patenting, or as barred by prior public use under 35 U.S.C. § 102. The court further finds that Defendants have failed to prove by clear and convincing evidence that the '382 patent is unenforceable due to inequitable conduct.

The court now issues its findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a):

FINDINGS OF FACT[1]

I. The Parties

1. Eli Lilly and Company is an Indiana corporation engaged in the business of research, development, manufacture,

1. Citations to the trial transcript will be "[witness name] Tr." followed by "[transcript page: line];" citations to the deposition testimony submitted by the parties will be "[witness name] Dep." followed by "[dep. page: line]"; citations to the trial exhibits will be "TX" followed by the exhibit number; citations to the file history of referenced patents will be "FH" followed by the page number; and citations to Lilly's demonstrative exhibits will be "LD" followed by the exhibit number.

and sale of pharmaceutical products throughout the world.

2. Lilly Industries Ltd., located in England, is a subsidiary of Eli Lilly and Company (the Plaintiffs are hereinafter collectively and individually "Lilly").

3. Zenith Goldline Pharmaceuticals, Inc. ("Zenith") is a Florida corporation having its corporate offices and principal place of business at 4400 Biscayne Boulevard, Miami, Florida 33137. Zenith's Amended Answer to Complaint for Patent Infringement, Affirmative Defenses and Counterclaims, filed August 7, 2002, P 3.

4. Dr. Reddy's Laboratories, Ltd. ("DRL") is a public limited liability corporation having its principal place of business at 7-1-27 Ameerpet, Hyderabad 500 016, India. DRL's Amended Answer and Counterclaim, filed July 29, 2002, P 3.

5. Teva Pharmaceuticals USA, Inc. ("Teva") is a Delaware corporation with its principal place of business at 650 Cathill Road, Sellersville, Pennsylvania. Answer of Defendant Teva Pharmaceuticals USA, Inc., filed on March 18, 2003, P 3.

6. On July 20, 1993, the United States Patent and Trademark Office ("PTO") issued the '382 patent which is entitled "2-Methyl-Thieno-Benzodiazepine." The '382 patent was assigned to, and is owned by, Lilly. TX 1000; TX 1360.

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7. The '382 patent claims, *inter alia*, the chemical compound known as olanzapine and methods of using olanzapine to treat schizophrenia. TX 1000, col. 12, claims 1, 2, 3, 7, 8, and 15.

8. Olanzapine, sold by Lilly under the trademark ZYPREXA(R) ("Zyprexa"), was approved by the United States Food and Drug Administration ("FDA") in late 1996. Paul Tr. 139:16-19.

9. Zenith, DRL, and Teva filed Abbreviated New Drug Applications ("ANDAs") under the Drug Price Competition and Patent Term Restoration Act of 1984, 98 Stat. 1585 (popularly known as the Hatch-Waxman Act), seeking approval to market generic copies of Lilly's olanzapine products prior to the expiration of the '382 patent.

10. Pursuant to 21 U.S.C. § 355(j)(2)(B)(ii), Zenith, DRL, and Teva sent letters to Lilly to notify it that they had filed ANDAs for olanzapine in various dosages.

11. Lilly filed suit against Zenith, DRL, and Teva alleging infringement of the '382 patent under 35 U.S.C. § 271(e)(2)(A). The court consolidated Lilly's suits against Zenith, DRL, and Teva into this single action. *See e.g.*, Entries of February 15, 2002; April 11, 2002; November 1, 2002; and March 14, 2003.

12. Lilly seeks an order (1) prohibiting FDA approval of the Defendants' generic olanzapine products prior to the expiration of the '382 patent, in accordance with

35 U.S.C. § 271(e)(4)(A); and (2) enjoining the Defendants from the commercial manufacture, use, offer to sell, sale, or importation of their olanzapine products, in accordance with 35 U.S.C. § 271(e)(4)(B). Complaint, filed April 2, 2001, Prayer for Relief.

13. After the commencement of the suit, Zenith and DRL stipulated that "if the Court finds the '382 patent valid and enforceable, then their actions constitute infringement." Entry, December 2, 2003 at 2. The parties further stipulated that the only method-of-use claims to be tried in this case are claims 7 and 8 of the '382 patent relating to the treatment of schizophrenia. Stipulation and Order entered on July 31, 2003 at p. 3. Therefore, the issues before the court are the validity and enforceability of claims 1, 2, 3, 7, 8, and 15 of the '382 patent.

14. Teva did not participate in the trial but agreed to be bound by the decision of the court herein. Entry on Joint Stipulation and Staying Actions. July 16, 2003.

II. Background in the Relevant Field Prior to the Prosecution of the '382 Patent

A. Schizophrenia

15. Schizophrenia is a chronic, debilitating mental illness that appears during late adolescence or early adulthood and essentially lasts the lifetime of the patient. Paul Tr. 109:17-110:1.

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16. Some of the symptoms of schizophrenia include, but are not limited to, "positive" symptoms and "negative" symptoms. "Positive" symptoms include hallucinations, delusions, and thought disorders. *See*, *e.g.*, video clip at TX 1446.1. "Negative symptoms" include loss of emotional and mental functioning, loss of motivation, loss of normal emotional response to other people, slowness of thinking, memory deficits, changes in speech (speaking in a dull monotone), and difficulties with cognition, sustained attention, decision-making, and mental flexibility. Paul Tr. 108:2-25, 109:1-16; Schulz Tr. 2972:1-5.

B. Early Drug Treatment — Typical Antipsychotic Drugs

17. Prior to the discovery of antipsychotic medications in the 1950s, most schizophrenic patients were isolated from society and kept in large asylums. Paul Tr. 110:10-19. This pattern of lifetime institutionalization for schizophrenic patients began to change in 1952 with the introduction of chloropromazine and continued through the later introduction of haloperidol in the 1960s. TX 1398 at 746; Paul Tr. 111:2-9. These early antipsychotic medications (known as "typical" antipsychotics) showed substantial reduction of positive symptoms and allowed a number of patients to leave institutional settings. TX 1398 at 746; Paul Tr. 111:12-112: 4.

18. However, the typical antipsychotic medications did little to treat the symptoms of schizophrenia and also

induced a number of "sometimes severe and intolerable neurological side effects." TX 1398 at 746; Paul Tr. 112:8-13. Such side effects associated with so-called extrapyramidal symptoms or "EPS" led to gross movement disorders, such as disfiguring tremors, stiffness, tics, and writhing. A particularly severe form of EPS, called "tardive dyskinesia," persisted even after medications were withdrawn. Paul Tr. 113:22-114:1. In addition, patients experienced elevation of the hormone prolactin that led to breast engorgement and. milk production in both male and female patients. Paul Tr. 112:5-115:12.

C. Clozapine: The First Atypical Antipsychotic

19. In the late 1960s and early 1970s, it became apparent that a drug called "clozapine" could treat the psychotic symptoms without EPS or prolactin elevation, causing it to be recognized as the first "atypical" antipsychotic: Paul Tr. 116:6-117:2; Nichols Tr. 2743:9-13.

20. In 1975, clozapine was withdrawn from the market in many countries because it was found to cause an often fatal blood disorder called "agranulocytosis" in approximately one percent of patients. This effect, and resulting withdrawal of the drug from the market, prompted people in the pharmaceutical industry to start looking for a drug like clozapine, but without the same side effect profile. Nichols Tr. 2743:14-2744:9; Paul Tr. 131:8-11; Schulz Tr. 3004:15-20.

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D. The Search for a Safe, Atypical Antipsychotic Drug

21. The general failure for many years to find a clozapine replacement was reflected in the scientific literature. TX 1356, Nichols Tr. 2750:17-2752:2. The literature contains many reports of promising compounds which failed either for lack of efficacy or because of toxic side effects. TX 1356; TX 1383; TX 1593; TX 1594; TX 1595; Nichols Tr. 2751:5-2769:24; *see also* Tupper Tr. 242:22-243:10, 246:9-247:8; TX 1595 (summarizing various scientific publications that reported the efforts of major pharmaceutical companies to find safe and effective antipsychotic medications).

22. In late 1989, the FDA approved clozapine for limited use in the United States notwithstanding its adverse side effects, as a therapy of last resort to be used only with careful blood monitoring. Paul Tr. 117:25-118:13.

23. In 1991, the New England Journal of Medicine reported that, "despite the extensive developmental effort in this area, no alternative to clozapine has been identified that has clinical antipsychotic efficacy and no extrapyramidal neurologic side effects, but has a low risk of inducing other important toxic effects (bone marrow suppression or seizures)." TX 1398 at 747.

24. Clozapine and certain other "typical" antipsychotics on the market such as chlorpromazine and haloperidol, had a "neuroleptic substituent," an electron withdrawing group believed to be important for antipsychotic activity. The most common neuroleptic substituent has

a halogen atom: The term "halogen" refers to either a fluorine or a chlorine atom. Tupper Tr. 414:9-418:18, 487:13-488:1.

E. Lilly's Attempts to Discover a Safe, Atypical Antipsychotic Drug

25. In the late 1970s and early 1980s, Lilly produced a novel class of compounds called thienobenzodiazepines. Tupper Tr. 428:23-429:25. Thienobenzodiazepines are tricyclic compounds having "thieno," "benzo," and "diazepine" rings fused together.

26. In 1975, Lilly filed a patent application related to these compounds. In 1978, the PTO issued two patents, U.S. Patent No. 4,115,568 ("the 568 patent"), TX 1408, and U.S. Patent No. 4,115,574 ("the 574 patent"), TX 3129, having identical technical disclosures, but different claims. Tupper Tr. 429:16-20, 431:4-19. Dr. Jiban Chakrabarti ("Dr. Chakrabarti") and Dr. David Tupper ("Dr. Tupper") are listed as the named inventors on the 568 patent and the 574 patent. TX 1408; TX 3129.

27. The 568 and 574 patents described the members of this class of new compounds as "useful in the treatment of . . . certain kinds of psychotic conditions . . ." TX 3129, col. 13,11. 62-66; TX 1408, col. 14, 11. 41-42.

28. The 574 patent identifies the characteristics of the most preferred class of compounds within this family. TX 3129, col. 4,11. 27-29. From this most preferred class, the patent identifies one particularly active compound

as 2-ethyl-7-fluoro-10-(4'-methyl-1'-piperazinyl)-4H-thieno[2,3-b][1,5]benzodiazepine, known throughout this trial as "ethyl flumezapine." Tupper Tr. 431:20-432:8.

29. Lilly, like many others in the field, modeled its lead candidates after clozapine, having a halogen atom in the molecule. Nichols Tr. 2751:5-2757:14; TX 1356 at 806; Tupper Tr. 413:21-414:9, 503:20-21; Pullar Tr. 200:20-201:3. Clozapine has a chlorine atom (Cl) at a position analogous to the fluorine atom (F) in ethyl flumezapine.

30. Other than the broad genus claimed in claim 1, Lilly's 574 patent claimed only compounds with a halogen. TX 3129, col. 39, claims 2-7; Tupper Tr. 433:5-14; Nichols Tr. 2749:5-9.

31. Beginning in the fall of 1974, Lilly made a compound like ethyl flumezapine, but without the fluorine atom, which corresponds to ethyl olanzapine, a compound otherwise known as "compound 222". Tupper Tr. 426:23-427:10; TX 1205.

32. From the very earliest tests of the ethyl flumezapine and compound 222 molecules, it was apparent that the fluorine-containing molecule (ethyl flumezapine) was much more active in tests believed to be relevant to potential antipsychotic activity than the molecule without the fluorine (compound 222). Tupper Tr. 428:9-15.

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33. After a year and a half of preclinical development work aimed at taking ethyl flumezapine into human clinical trials, disaster struck. In a six-month toxicology study with dogs, conducted at 4, 8, and 12 mg/kg using three dogs of each sex at each dose level, blood disorders, reminiscent of the potentially fatal blood disorder seen with clozapine in humans, were seen in dogs at all dose levels. TX 1035; TX 3421; Pullar Tr. 175:14-176:23. In particular, the toxicology tests in dogs showed widespread neutropenias in all dose groups and one anemia. Neutropenia is a reduction of white blood cells. Some of the dogs had reductions as much as 75% of their normal value. TX 3421; Emmerson Tr. 542:6-21.

34. In an effort to find a compound in the class free of this problem, Lilly conducted a comparative toxicology test between ethyl flumezapine and a closely related compound called "flumezapine." TX 1003; Pullar Tr. 177:23-178:14. The difference between ethyl flumezapine and flumezapine is that in the two position on the thiophene ring where ethyl flumezapine has an ethyl group (-CH[2]-CH[3]), flumezapine has a methyl group (-CH[3]). Pullar Tr. 178:1-7.

35. During the comparative dog study, two of the ethyl flumezapine-treated dogs, but none of the flumezapine-treated dogs, developed blood problems. Pullar Tr. 180:11-19; TX 1003, 1004. As a result, Lilly terminated the development of ethyl flumezapine and commenced the development of flumezapine in early 1978 under the guidance of Dr. Ian Pullar ("Dr. Pullar"). Pullar Tr. 180:23-181:1; Hotten Dep. 71:12-72:10.

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36. Lilly spent the next four years developing flumezapine through preclinical testing and initial safety testing in normal human volunteers. Pullar Tr. 185:20-188:12; TX 1008; TX 1010. Among other tests, Lilly conducted a six-month dog study of flumezapine, Emmerson Tr. 544:23-545:24; TX 1005, and a safety trial in normal human volunteers. TX 1010 at ZYP 177 1715-19. Then, in the spring of 1982, during the first trial of flumezapine in actual schizophrenic patients, administered at and below therapeutic doses, several patients experienced elevations in the muscle enzyme creatinine phosphokinase (or "CPK") and in a variety of liver enzymes. Pullar Tr. 188:13-189:14, 195:15-198:16; TX 1015 at ZYP 177 1998-99; Hotten Dep. 70:14-71:11.

37. The findings were reported by telephone to the FDA. TX 3259. That afternoon, Dr. Paul Leber in the Division of Neuropharmacology Drug Products at the FDA, halted U.S. clinical testing when he "advised that patients be withdrawn from the drug as soon as possible." TX 3260.

38. Similarly, the British regulatory authority "expressed surprise at the magnitude of the increases in liver enzymes and especially the levels of CPK," noting that they "had not experienced anything similar." TX 1615. After Lilly informed the agency of these results, the agency withdrew the United Kingdom ("U.K.") authorization for clinical testing, and Lilly terminated the flumezapine clinical trials. Pullar Tr. 190:20-194:11; TX 1042.

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39. Neither the failure of the flumezapine clinical trials nor the reasons for it (muscle or liver enzyme elevations) were publicly reported. Reith Tr. 927:9-11; Nichols Tr. 2776:18-2777:3; TX 1356 at 809.

F. The Discovery of Olanzapine

40. After the failure of flumezapine in clinical trials, a team led by Dr. Tupper at Lilly created another group of compounds in the same series in an effort to find another compound that could be developed as a clozapine replacement and that would not meet the same fate in the clinic as flumezapine. Tupper Tr. 441:23-443:2, 446:2-447:17; TX 1229-40.

41. The cause of flumezapine's toxicity was unknown. Tupper Tr. 443:3-20. Speculation abounded inside Lilly regarding possible causes, including reactions involving the "piperazine nitrogen" and the fluorine atom.

> The distal piperazine nitrogen is demethylated and the nitrogen and adjacent carbon oxidised as with other N-methylpiperazinyl compounds. If this is the source of the toxicity it is unlikely that it can be reduced without losing the neuroleptic activity. The 7-fluorine is replaced by hydroxy and methylthio groups . . . . whether the source of this toxicity is the reduction in glutathione levels, a metabolic intermediate or the methylthio metabolite itself is at present, unknown. The hydroxylation metabolic pathway could also be implicated.

TX 3657 at ZY 80 94.

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42. Compounds with ethyl groups (like ethyl flumezapine and ethyl olanzapine (compound 222)) were not considered for further development because the ethyl group was believed by some at Lilly to produce agranulocytosis in dogs. TX 3657 at ZY 80 94; Tupper Tr. 443:6-444:20; Hotten Dep. 79:6-80:8, 81:11-19.

43. Several fluorinated and unfluorinated alternatives were made and tested, including the compound known as olanzapine (then known simply as "LY170053"). Hotten Dep. 42:5-16, 43:20-44:8, 45:1-17. Olanzapine was first synthesized in the U.K. by Terrence Hotten ("Mr. Hotten"), a research chemist at Lilly, on April 29, 1982. Tupper Tr. 446:2-14; TX 1229.

44. Olanzapine differs from flumezapine by having a hydrogen atom (conventionally not shown on structural diagrams) where flumezapine has a fluorine atom. Pullar Tr. 199:16-24; Hotten Dep. at 42:21-43:6. A number of people doubted that olanzapine would work because it lacked the halogen atom then known to be important to the activity of clozapine and believed to be important for activity in this series of compounds as well. Pullar Tr. 200:20-201:3; Tupper Tr. 451:7-20. Indeed, olanzapine was believed, based on a variety of preclinical tests, to be only about half as potent as flumezapine. Pullar Tr. 201:10-18; Tye Dep. 71:21-72:21, 75:21-76:12; TX 3657 at ZY 80 100-101,103 (comparing two compounds).

45. In 1983, Lilly began by testing olanzapine in dogs — first in a three-month study and later in a one-year study.

Emmerson Tr. 546:23-547-6, 552:14-17. During each of the studies, one dog developed a blood problem. Emmerson Tr. 546:19-24, 552:18-553:7. After extensive testing, Lilly determined that the effect in dogs appeared to be an immune response and "idiosyncratic" in nature, meaning it occurred due to the unusual sensitivity in individual dogs. Emmerson Tr. 549:22-550:23, 554:18-555:15. Only then did Lilly determine that it might cautiously proceed with human trials of olanzapine. Emmerson Tr. 550:14-551:8, 555:6-15.

46. In 1986 and 1987, Lilly conducted Phase 1 clinical trials of olanzapine in healthy human volunteers in Indianapolis, Indiana. Goldberg Tr. 307:9-21; TX 3741; TX 3742; TX 3744. At the conclusion of these trials, Lilly proceeded to the litmus test of olanzapine — a clinical trial to test the compound's efficacy in actual schizophrenic patients. Goldberg Tr. 326:25-327:20. These clinical trials took place in the U.K. TX 1058; TX 1064.

47. Toward the end of 1989, the clinical trials were promising. In the first test of the drug in actual schizophrenic patients, olanzapine appeared to be a safe and effective, atypical antipsychotic drug having a more favorable side effect profile than typical antipsychotics in terms of EPS and not producing the blood disorders in patients. Goldberg Tr. 335:19-20, 344:14-22, 345:6-9; TX 1063; TX 1064 at ZYP 520 983-84.

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48. On January 18, 1990, the olanzapine project team reported the success of the clinical trial to Lilly's Research Management Staff ("RMS"), and the RMS agreed to "product commitment." TX 1063 at ZYP 449 1132. After the project team report, the project was referred to with words like "AAA priority" and the "Manhattan Project" (in reference to the scientific push to develop the atom bomb), TX 3532, and Lilly scientists made plans for expanded clinical trials on the compound. Goldberg Tr. 338:21-340:7; TX 1063 at ZY 449 1128.

49. In the fall of 1990, Lilly conducted another comparative dog toxicology study prior to filing a patent application with the PTO. The study was designated D07290, and is known throughout this litigation as the "D07290 Dog Study" or "D07290 Study."

50. The purpose of the D07290 Study was to determine over the course of a chronic treatment period whether there was a difference in the toxicity profile between olanzapine and compound 222. Symanowski Tr. 664:4-665:13, 668:24-669:4, 2077:9-18; TX 3439 at ZYP 187 713, Item 4.

51. At the conclusion of the D07290 Study, Lilly claimed that the results of the study showed that olanzapine was unexpectedly superior to compound '222 in that olanzapine did not cause a significant elevation in average mean cholesterol versus compound '222. TX 1001.1 at FH 17-18.

52. The D07290 Dog Study is at the heart of this case and is discussed at length in this opinion.

III. Prosecution History of the '382 Patent

A. The 143 Patent Application

53. On April 23, 1991, Lilly filed U.S. Application Serial No. 690,143 ("the 143 application"). TX 1000, col. 1, 11. 4-5.

54. Lilly had previously filed a patent application in the U.K. on April 25,1990, and perfected the priority date. Pursuant to 35 U.S.C. § 119, Lilly is entitled to the April 25, 1990 date for purposes of determining the relevant scope and content of the prior art. Killworth Tr. 769:15-770:16, TX 1000.

55. As part of the 143 patent application, Lilly was required to fill out an Information Disclosure Statement ("IDS") to inform the Patent Examiner ("Examiner") of the most closely related prior art. In Lilly's IDS, Charles Ashbrook ("Mr. Ashbrook"), Assistant General Patent Counsel at Lilly, represented that the most closely related prior art was the matter claimed in the 568 patent. TX 1001.1 at FH 44-45.

56. Though the patent applicants did not cite the Examiner to either the 574 patent or Chakrabarti et al., *4-Piperazinyl-10H-thieno[2,3-b][1,5]benzodiazepines as Potential Neuroleptics*, J. MED. CHEM. 23:878-84 (1980) ("*Chakrabarti 1980a*"), the Examiner performed a search of the prior art, found those references, and cited them in the Office Action. TX 1001.1 at FH 48-53.

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57. In the 1991 IDS, Lilly told the Examiner that compound 222, described in the 568 patent, is the adjacent homolog to olanzapine, but that olanzapine is patentable over the disclosure in the 568 patent because of the "surprising biological differences of the 2-methyl derivative (olanzapine) over the 2-ethyl derivative (compound 222)." TX 1001.1 at FH 44.

58. Also in the 1991 IDS, the patent applicants told the Examiner that flumezapine, which is the 7-fluoro derivative of olanzapine, "caused significant adverse effects. when administered to humans" and that olanzapine "has an unexpectedly superior therapeutic profile." TX 1001.1 at 45.

59. In the 143 application, the applicants represented that: "In dog toxicity studies with a closely analogous compound 2-ethyl-10-(4-methyl-1-piperazinyl)-4H-thieno[2,3-b][1,5] benzodiazepine [compound 222], at a dosage of 8 mg/kg, it was observed that four out of eight dogs showed a significant rise in cholesterol levels, whereas the compound of the invention did not show any rise in cholesterol levels." TX 1001.1 at FH 17-18. This text corresponds to col. 3, 11. 29-36 of the '382 patent, TX 1000, col. 3,11. 29-36, and is a reference to the D07290 Dog Study. Plaintiffs' Reply to Amended Answer to Complaint for Patent Infringement, Affirmative Defenses, And Counterclaims of Zenith Goldline Pharmaceuticals, Inc. (filed September 20, 2002) ("Lilly's Reply"), P 19.

60. In the 143 application, Lilly stated that seventeen patients received flumezapine before the clinical trial was terminated after consultation with the FDA because of an unacceptably high incidence of raised enzyme levels in the treated patients. Specifically, "creatinine phosphokinase (CPK) and the liver enzymes, serum glutamate oxalacetic transmaninase (SGOT) and serum glutamate pyruvate transaminase (SGPT), estimated in the blood samples from the patients, were substantially in excess of normal values, indicating the possibility of toxicity." TX 1001.1 at FH 15. With respect to olanzapine, Lilly stated only that "there is a low incidence of only mild and transient elevation of liver enzymes in patients treated with therapeutic doses, and plasma levels of . . . CPK are lower than with flumezapine, indicating a lower adverse effect on muscular tissue." TX 1001.1 at FH 17.

61. The Examiner reviewed the claims for compliance with the enablement requirement of 35 U.S.C. § 112, the definiteness requirements of 35 U.S.C. § 112, for novelty under 35 U.S.C. § 102, for nonobviousness under 35 U.S.C. § 103, and for obviousness-type double patenting. TX 1001.1 at FH 49-51, 53; Killworth Tr. 778:10-24, 779:5-21, 781:13-19.

62. On November 25, 1991, the Examiner issued an Office Action with respect to the '143 application rejecting all of the claims. TX 1001.1 at FH 48-53.

63. In evaluating novelty, the Examiner rejected Lilly's claims under 35 U.S.C. § 102(b) as being "anticipated"

by the 574 patent, citing a portion of the text of the 574 patent that was shared by the 568 patent cited by Mr. Ashbrook in his IDS. Killworth 778:20-779:3; TX 1001.1 at FH 50.

64. The Examiner rejected all of the claims under 35 U.S.C. § 103 as obvious over the 574 patent in view of *Chakrabarti 1980a*. TX 1001.1 at FH 51-53. The Examiner stated that "it would have been obvious to one with ordinary skill in the art toreplace the 2-ethyl substituent on the homologous species [compound 222] taught in [the 574 patent] with the 2-methyl substituent in order to obtain the instant compound [olanzapine] because [*Chakrabarti 1980a*] specifically suggests to one with ordinary skill in the art that this type of substituent is preferably [*sic*] to increase [central nervous system] activity." TX 1001.1 at FH 51-52.

65. The Examiner considered the description of the unexpected cholesterol results in the application to be "insufficient" because "1) no controls were run, 2) there is no evidence that such data is statistically significant and 3) that such data is necessarily showing a significant beneficial effect to the patient." TX 1001.1 at FH 52; Killworth Tr. 780:10-17.

66. Finally, the Examiner rejected Lilly's claims under the judicially created doctrine of "obviousness-type double patenting" as being unpatentable over the claims of the 574 patent in view of *Chakrabarti 1980a* for the same reasons that the claims were alleged to be obvious from the text of the 574 patent in view *of Chakrabarti 1980a* under 35 U.S.C. § 103. TX 1001.1 at FH 53; Killworth Tr. 781:13-782:12.

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B. The 348 Continuation Application

67. Lilly responded to the Office Action on May 22, 1992, by filing a file wrapper continuation application to extend the time period for response to the rejection. TX 1001.1 at FH 98-100; Killworth Tr. 782:16-783:13. This application was assigned the application serial number 890,348 (the "348 application"). TX 1001.1 at FH 98.

68. The 348 application contained the same disclosure, including the claims, as the 143 application. In accordance with standard PTO procedure, the 348 application was assigned to the same Examiner who had examined the 143 application. Killworth Tr. 782:16-783:25; TX 1001.1 at FH 98-100.

69. On September 11, 1992, the Examiner issued another Office Action rejecting the claims for the same reasons set forth in the prior Office Action in the 143 application. Killworth Tr. 784:1-22; TX 1001.1 at FH 102.

70. On December 10, 1992, three representatives of Lilly conducted a personal interview with the Examiner in the 348 application. The Lilly representatives were Macharri Vorndran-Jones ("Ms. Vorndran-Jones") and Joseph Jones ("Mr. Jones") from Lilly's legal department, and Dr. James Emmerson ("Dr. Emmerson"), a Lilly toxicologist. TX 1001.1 at FH 109-10.

71. At the interview, Lilly presented eight declarations of Lilly employees to the Examiner extensively describing the results of comparative tests of olanzapine and

compound 222, including the D07290 Dog Study. TX 1001.1 at FH 125-54.

72. These declarations were submitted by Dr. Nicholas Tye ("Dr. Tye"), Dr. Pullar, Dr. Nicholas Moore ("Dr. Moore"), Dr. Jeffrey Means ("Dr. Means"), Dr. Emmerson, Dr. David Wong ("Dr. Wong"), Dr. David Scruby ("Dr. Scruby"), and Dr. James Symanowski ("Dr. Symanowski"). TX 1001.1 at FH 125-27 (Tye), FH 128-30 (Pullar), FH 131-34 (Moore), FH 135-39 (Means), FH 140-42 (Emmerson), FH 143-45 (Wong), FH 146-48 (Scruby), FH 149-54 (Symanowski). Dr. Tye, Dr. Pullar, and Dr. Moore are pharmacologists; Dr. Means is a pharmacologist and toxicologist; Dr. Emmerson, as stated earlier, is a toxicologist; Dr. Wong is a biochemist; Dr. Scruby is a Lilly physician; and Dr. Symanowski is a statistician.

73. All declarations were submitted under 37 C.F.R. § 1.132 and all declarants swore that the statements made therein were true. TX 1001.1 at FH 125-54.

74. Dr. Moore's declaration analyzed the results of behavioral tests in which animals were administered olanzapine or compound 222. TX 1001.1 at FH 131-34. Dr. Moore concluded that in the conditioned avoidance response ("CAR") test, olanzapine was more active. TX 1001.1 at 132. He also concluded that out of the four tests he conducted — the apomorphine-induced climbing and hypothermia tests in mice, the CAR test in rats, the catalepsy-induction in rats, and the locomotor activity in rats — "both compounds have

very similar dopamine antagonist activity *in vivo.*[2]" TX 1001.1 at 134.

75. Dr. Pullar presented the results of *in vitro* testing of olanzapine and compound 222 using binding assay tests. The results were presented in two tables showing the respective IC[50] values for each compound in each of the tests. No argument was made that the compounds could be differentiated based on the results of these tests. TX 1001.1 at FH 128-30.

76. Dr. Tye's declaration discussed his examination of the data set out by Dr. Moore and Dr. Pullar and his views on the D07290 Dog Study carried out by Dr. Means and the results thereof. TX 1001.1 at FH 124-27. Dr. Tye concluded that: (1) the data of Dr. Moore and Dr. Pullar suggested "little difference in the properties of [olanzapine and compound 222]"; (2) the data from the dog toxicology study "showed significantly increased levels of cholesterol in the case of [compound 222]," (3) raised cholesterol levels resulting from compound 222 are a serious disadvantage because cholesterol is a factor in coronary heart disease in humans, and (4) olanzapine "is clearly and significantly superior to [compound 222] so far as it has been shown in the toxicity study by Dr. Means to lack any tendency to raise cholesterol levels." TX 1001.1 at FH 126.

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2. As used in this case, the term "in *vivo*" refers to the results observed in animals, and the term "*in vitro*" refers to the results observed in a laboratory.

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77. Dr. Wong's declaration evaluated data obtained from radioligand and binding studies of olanzapine and compound 222. TX 1001.1 at FH 143-45. In part, Dr. Wong concluded that "both olanzapine and [compound] 222 can produce functional responses at 5-HT[1C] and 5-HT[2] receptors." TX 1001.1 at FH 145.

78. Dr. Emmerson oversaw the Lilly D07290 Dog Study. He stated in his declaration that he believed that "olanzapine displayed an unexpected and significant superior toxicological benefit over compound 222" with respect to the elevation of serum cholesterol in female dogs dosed with 8 mg/kg of compound 222 compared with dogs similarly dosed with olanzapine and the control dogs. TX 1001.1 at FH 142. Dr. Emmerson believed that this toxicological benefit was a critical property to consider in the safety analysis of the two compounds and that he "would not recommend the clinical development of a compound which significantly increases the serum cholesterol levels in dogs when there is a compound with similar activity which does not affect serum cholesterol levels." TX 1001.1 at FH 142.

79. Dr. Means was the study director for Lilly's D07290 Dog Study. His declaration summarized the design, conduct, and findings of the study. TX 1001.1 at FH 134-39.

    a. Dr. Means stated that "suprisingly serum cholesterol levels in females of the 8 mg/kg-'222 treatment group were significantly

increased when compared to the cholesterol levels of females in either the 8 mg/kg-olanzapine treatment group or the control group." TX 1001.1 at FH 137.

b. Dr. Means also stated that "no significant differences in serum cholesterol levels were detected among the olanzapine treatment and control groups." TX 1001.1 at FH 137.

c. Dr. Means concluded that "the toxicity of olanzapine and compound 222 in beagle dogs is similar in many respects," but that "an unexpected difference between olanzapine and compound 222 was the significant increase of serum cholesterol concentrations with time in female dogs given 8 mg/kg/day of compound 222 compared to the cholesterol values in female dogs given 8 mg/kg/day [of] olanzapine and compared to the cholesterol values in female control dogs." TX 1001.1 at FH 139.

80. Dr. Scruby stated that he reviewed Dr. Means' and Dr. Symanowski's declarations, and that those declarations provided the basis for Dr. Scruby's clinical statements concerning the dog toxicology studies. TX 1001.1 at FH 146-48.

a. In his declaration, Dr. Scruby discussed his knowledge of the risk associated with elevated total cholesterol in humans and

stated that "any factor which leads to an increase in serum lipids [] can have a significant deleterious effect on [cornary artery disease and the progression of atherosclerosis]." TX 1001.1 at FH 147-48.

b. Dr. Scruby concluded that based on the findings of the study in which the serum cholesterol female dogs treated with compound 222 after 60 days averaged nearly 260mg/dl and "in view of the overwhelming evidence in the literature that serum cholesterol in excess of 240 mg/dl is a significant contributor to the genesis of atherosclerosis," he believed that "the significant elevation of serum cholesterol observed in female dogs treated with the 222 compound could provide a marked clinical difference in the pathogenesis of coronary artery disease." TX 1001.1 at FH 148.

81. Dr. Symanowski's declaration summarized the statistical tests used in the D07290 Study. TX 1001.1 at FH 149-54. He reported that cholesterol levels in 8 mg/kg compound 222 female dogs were noticeably elevated after day 25 of treatment and that statistical analysis indicated that these levels increased significantly over time when compared to both the 8 mg/kg olanzapine female dogs and the control group, whereas none of the olanzapine-treated groups were statistically significantly different from control.

TX 1001.1 at FH 150-51. He presented three graphs illustrating mean cholesterol levels over time. Figure 1 presented the group mean cholesterol values throughout the study for all of the groups of female dogs. TX 1001.1 at FH 152. Figure 2 presented the same information for the groups of male dogs. TX 1001.1 at FH 153. The data presented by Dr. Symanowski showed no significant difference between olanzapine and compound 222 with respect to cholesterol in male or low-dose female dogs. Figure 3 illustrated the mean values plus and minus one standard error for the cholesterol levels in female dogs dosed with 8 mg/kg of compound 222 and olanzapine, as well as the female control group. TX 1001.1 at FH 154.

82. Following the interview, the Examiner prepared a short, handwritten summary of the interview indicating that the Lilly representatives and the Examiner discussed the declarations. TX 1001.1 at FH 109. The Examiner reported in his summary that while "the reviewed data looked sufficient pending final review and analysis of the complete set of data," an agreement was not reached as to patentability. TX 1001.1 at FH 109.

83. Following the interview, the patent applicants presented to the PTO a document entitled "Response After Final." TX 1001.1 at FH 112-24.

84. In the Response After Final, the patent applicants argued that "olanzapine exhibits the significant beneficial property of preserving the natural balance of cholesterol

synthesis in the treatment of schizophrenia and schizophreniform disorders." TX 1001.1 at FH 119-20.

85. In the Response After Final, the patent applicants also argued that Lilly's "probative evidence of olanzapine's superiority in one or more properties is sufficient to overcome the *prima facie* obviousness rejection." TX 1001.1 at FH 120.

86. To overcome a prima facie obviousness rejection, a patent applicant can respond to the rejection or the applicant can attempt to overcome the rejection by filing declaratory evidence. Sofocleous Tr. 959:15-960:6; Killworth Tr. 789:4-16.

87. While Lilly did not acquiesce to the Examiner's determination that the claims were prima facie obvious, it did not advance specific argument to challenge this finding. TX 1001.1 at FH 117, 124 (indicating Lilly's intent not to admit prima facie obviousness); Vorndran-Jones Tr. 1611:3-7; Killworth Tr. 789:4-790:2; Sofocleous Tr. 789:15-22.

88. In the Response After Final, Lilly made several significant statements.

    a. "Dr. Means' Declaration demonstrates that the blood cholesterol levels of female dogs treated with the '222 derivative were significantly elevated when compared to the blood cholesterol levels of dogs treated with the 2-methyl (olanzapine) compound." TX 1001.1 at FH 120-21.

b. "No significant increase in cholesterol levels was observed in either the olanzapine treated dogs or the control dogs." TX 1001.1 at FH 120.

c. "Valid controls were included in the study as substantiated by Dr. Means', Dr. Emmerson's, and Dr. Symanowski's Declarations." TX 1001.1 at FH 121.

d. "Statistically significant elevated blood cholesterol levels occurred in the '222 treated dogs, as demonstrated by Dr. Symanowski's Declaration." TX 1001.1 at 121.

e. "Dr. Tye declares that pharmacologically there is little difference. between olanzapine and '222; however, he states that olanzapine is clearly and significantly superior to the '222 compound based on olanzapine's toxicological benefit." TX 1001.1 at FH 122.

89. On December 17, 1992, the Examiner issued a Notice of Allowability of all of the pending claims of the '382 patent, meaning that he had determined that the requirements for patentability had been met and that all previous rejections were withdrawn. TX 1001.1 at FH 156.

90. The Examiner noted that the Notice of Allowability was in response to "Amendment B [Lilly's Response After Final] and the declarations filed 12/10/92." TX 1001.1 at FH 156; Killworth Tr. 792:16, 793:16.

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91. On July 20, 1993, the PTO issued the '382 patent. TX 1000; TX 1360. The named inventors are Dr. Chakrabarti, Dr. Tupper, and Mr. Hotten.

IV. The Validity of the '382 Patent

A. Anticipation

1. Anticipation by *Chakrabarti 1980a*

92. Defendants argue the claims of the '382 patent are anticipated by *Chakrabarti 1980a.* One of the authors of that scientific article is Dr. Chakrabarti of Lilly. TX3465.

93. The *Chakrabarti 1980a* publication describes several variations of the 4-piperazinyl-10H-thieno[2,3-b][1,5]benzodiazepine family of compounds and examines specifically three areas on the structure of the family of molecules. TX 3465; Reith Tr. 820:14-821:10; 827:18-828:3.

94. All compounds examined in *Chakrabarti 1980a* had a common structural nucleus with different substitutions at three places: the piperazine ring, the benzene ring, and the thiophene ring. TX 3465; Reith Tr. 827:18-828:3. The authors labeled these three areas for substitution "R", "R[1]", and "R[2]". TX 3465.

95. Only particular substituents for each disclosed compound are listed in a table. TX 3465 at 880-82.

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96. In total the authors examined forty-five specific compounds (as opposed to a genus of compounds) in the 4-piperazinyl-10H-thieno[2,3-b][1,5]benzo diazepine family and 14 analogous 5-piperazinyl-substituted 4H-thieno[2,3-b][1,4]benzodiazepines, created "to compare the activity." TX 3465 at 879, 880-82. Significantly, olanzapine was not one of the compounds the authors examined. TX 3465; Reith Tr. 828:7-9.

97. To arrive at their conclusions about which compounds were preferred, the authors tested the compounds by using three different animal behavioral tests: the mouse hypothermia test, the CAR test, and the rat catalepsy ("CAT") test. TX 3465; Reith Tr. 821:16-826:5. Of these, the tests of special interest were the CAR and the CAT test. Pullar Tr. 254:4-11.

98. The CAR test evaluates the inhibition of a behavioral response in rats. Reith Tr. 822:19-823:13. In this test, inhibition is expressed on a scale from zero to five where a score of zero reflects minor inhibition, and a score of five represents severe inhibition. Reith Tr. 823:8-13.

99. The CAR test was the only measure of potential antipsychotic activity, and if the compound did not achieve a CAR score of three or four at a dose of less than 30 mg/kg, it was not considered active. Nichols Tr. 2768:16-2769:11.

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100. A "good score" in the CAR test — a three or four — indicates a desirable blockade of dopamine receptors. Reith Tr. 823:22-24; Pullar Tr. 222:25-223:1. Clozapine, the benchmark compound, had a CAR score of three. LaVoie Tr. 1568:11-15.

101. The CAT test evaluates cataleptic behavior in rats following administration of a compound. The scores in this test reflect group scores, with a group consisting of eight animals. The higher the score the more catalepsy observed in the group. Reith Tr. 824:8-825:16.

102. Generally, for purposes of determining whether a compound has the potential to be an effective atypical antipsychotic, a scientist would like to see a "separation of activity" — i.e., a good score on the CAR test at a dose that would not get a high score on the CAT test. Reith Tr. 826:6-23; Pullar Tr. 254:4-15.

103. However, a separation between the CAR and CAT scores only came into play if the first condition — a good CAR score — was met. Moore Dep. 82:5-22, 83:9-84:6, 86:5-14. The separation of activity between the CAR and CAT scores was thought to be relevant to the potential absence of EPS at an active or potentially therapeutic dose. The separation, by itself, is not a measure of activity. Moore Dep. 83:9-84:6, 86:5-14.

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104. *Chakrabarti 1980a* identified five specific compounds (9, 12, 17, 29, and 34) that were "found to be more potent than clozapine and show similar, if less marked, separation of activity in [the CAR and CAT] tests." TX 3465 at 878, 883.

105. The five preferred compounds had a CAR score of three or better. LaVoie Tr. 1568:16-18.

106. With respect to these five preferred compounds, the authors expressed a preference for specific, complete compounds; they did not express a preference for a genus of compounds having any and all combinations of the individual substituents on those molecules. Nichols Tr. 2779:2-8 ("[A] preferred compound would have a combination of different substituents that would lead it to have optimal activity. Removing one or more of those substituents would destroy that preference. So the compound would be taken as a whole."); LaVoie Tr. 1567:11-19.

107. Four of the five preferred compounds (9, 12, 17, and 29) have a fluorine at the 7-position of the benzene ring (compound 29 contains two fluorine atoms, one at the 7-position and one at the 8-position). Tupper Tr. 437:4-11; Nichols Tr. 2749:9-18, 2780:2-9; TX 3465 at 880-81. The fifth, compound 34, does not contain a fluorine on the benzene ring, but contains a hydroxyethyl group on the piperazine ring. Tupper Tr. 437:12-16; Nichols Tr. 2749:9-18, 2780:11-19; TX 3465 at 881. These two components were generally recognized at the time of the publication of

Chakrabarti 1980a to enhance antipsychotic activity. LaVoie Tr. 1564:6-1565:4; Nichols Tr. 2785:18-2787:22; TX 3123 at 396-97. Olanzapine does not include either of these substituents. Reith Tr. 902:5-8; LaVoie Tr. 1564:16-18.

108. The authors did not list compound 6, the freebase of compound '222, as a preferred compound. TX 3465. Compound 6 had a CAR score of two. TX 3465 at 880; LaVoie Tr. 1568:11-15.

109. In addition to the preferred compounds, the authors discussed the authors' preferred substituents. Reith Tr. 897:6-12. For example, the authors expressed a preference for position 7 by stating that "the substitution of the phenyl ring with a halogen atom (Cl, F) at position 7 enhanced the activity" and that the "7,8-difluoro compound (29) retained good activity." TX 3465 at 879, col. 2. The text never states a preference for a hydrogen at position 7, as is required for olanzapine. In addition, the authors mentioned three specific substituent groups thought to be helpful: three R groups (methyl, hydroxyethyl, and hydroxypropyl), three R[1] substitutions (7-F, 7-Cl, 7,8-di-F, explained above), and three R[2] groups (2-methyl, 2-ethyl, and 2-isopropyl).[3] TX 3465 at 879. No possible combination of these preferred substituents, i.e., a preferred R with a preferred R[1] and a preferred R2, would generate olanzapine

3. R corresponds to the piperazine ring at the upper right of the molecule, R[1] to position 7, and R[2] to position 2. *See* TX 3465 at 880, figure labeled "1-45"; Reith Tr. 831:2-3, 833:5-18, 840:23-25.

because all of these combinations contain a fluorine (F) or a chlorine (Cl) atom at position 7 where olanzapine has only a hydrogen. Reith Tr. 897:16-898:21; LaVoie Tr. 1566:2-12; Nichols Tr. 2777:4-2778:6; TX 3465 at 879.

110. Because none of the forty-five specific compounds disclosed in *Chakrabarti 1980a* include olanzapine, none of the five preferred compounds disclosed in *Chakrabarti 1980a* include olanzapine, and none of the preferred substituents include a hydrogen at position 7 as is required for olanzapine, the court finds *Chakrabarti 1980a* does not describe olanzapine.

111. The court further finds that one of ordinary skill in the art, applying the preferences expressed in *Chakrabarti 1980a*, would not envision olanzapine.

112. The composition and method claims of the '382 patent are directed to dosage forms containing specified amounts of olanzapine (e.g., claim 15) and methods of treating patients suffering from schizophrenia with specified doses of olanzapine (e.g., claim 8). Such dosage forms and methods are not described in *Chakrabarti 1980a* for any of the compounds disclosed in that article. *See* Findings of Fact # # 183-84.

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2. Anticipation by *Schauzu*

113. DRL also argues that olanzapine is described as compound 11 in a scientific article entitled Schauzu, H.G. and Mager, P.P., *A Free-Wilson Study of 4-Piperazinyl-10H-thienobenzodiazepine Analogues*, 38 DIE PHARMAZIE 562 (1983) (*"Schauzu"*).

114. The biological data in *Schauzu* comes from Chakrabarti, J.K., *et al.*, *Effects of Conformationally Restricted 4-Piperazinyl-10H-thienobenzodiazepine Neuroleptics on Central Dopaminergic and Cholinergic Systems*, J. MED. CHEM. 1133(1982) ("*Chakrabarti 1982*"). Nichols Tr. 2793:20-2794:9; LaVoie Tr. 1506:9-18; Reith Tr. 902:9-20.

115. The compounds disclosed in *Chakrabarti 1982* were fluorinated piperazine compounds. This means that the compounds had a fluorine in the 7-position and two nitrogens in the top ring (the piperazine ring). Nichols Tr. 2793:7-16.

116. The structure drawn in *Schauzu* is not a fluorinated piperazine compound because it is missing both a fluorine atom at the 7-position and one of the nitrogen atoms in the top ring. Nichols Tr. 2792:22-2795:19. Thus, the structure drawn in *Schauzu* is a piperidine compound — not a piperazine as the title of the article otherwise sets forth. LaVoie Tr. 1532:5-19; Nichols Tr. 2789:3-23.

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117. A piperidine compound has one nitrogen in the top ring (the piperidine ring), whereas a piperazine compound, as noted above, includes a second nitrogen" substituent in the top ring (the piperazine ring). Nichols Tr. 2789:16-2790:1; LaVoie Tr. 1500:16-1501:10.

118. *Schauzu* was abstracted by both *Chemical Abstracts* and *Beilstein* as disclosing piperidine compounds. Nichols Tr. 2791:10-2792:18; LaVoie Tr. 1532:3-1535:17.

119. Olanzapine is a piperazine compound. Nichols Tr. 2795:12-16.

120. The structure drawn in *Schauzu* does not include olanzapine since the structure does not include a second nitrogen in the top ring. Nichols Tr. 2792:22-2795:19.

121. The biological data from *Chakrabarti 1982* does not include olanzapine because olanzapine is an *unflourinated* piperazine compound. Nichols Tr. 2789:24-2790:1, 2795:12-16.

122. In order to find that olanzapine is described as compound 11 in *Schauzu*, one with ordinary skill in the art would have to mentally insert a nitrogen atom into the structure depicted in *Schauzu*, thereby converting it into a piperazine compound (in this case, olanzapine), yet ignore the fact that the biological data reported in the *Schauzu* article was from *Chakrabarti*

1982, which discussed only fluorinated compounds. *Compare* LaVoie Tr. 1500:20-1501:2, 1504:4-1507:5, *with* Nichols Tr. 2793:20-2794:9, 2789:16-2790:1; Reith Tr. 902:9-20.

123. Olanzapine is not described as compound 11 in *Schauzu.* Nichols Tr. 2789:3-5.

B. Obviousness

124. Lilly contends the discovery of olanzapine and its unique properties represent a nonobvious selection invention within the broad genus of compounds disclosed in the '574 and '568 patent. In other words, the '382 patent, which specifically claims olanzapine, is a "species" falling within the broad "genus" claimed in the '574 patent. Defendants contend that the claims of the '382 patent are obvious under 35 U.S.C. § 103 over the disclosure of olanzapine in the '574 patent in combination with *Chakrabarti 1980a.* They also contend the claims of the '382 patent are obvious over the disclosure of flumezapine in the '574 patent in combination with *Chakrabarti 1980a* and the *Sullivan and Franklin* article discussed infra., Findings of Fact § IV.B.1.d.

Appendix B

1. The Scope and Content of the Prior Art

a. Clozapine and Clozapine-Like Molecules

125. The prior art included numerous failures to find a safe, atypical antipsychotic drug. *See* Findings of Fact § II.D.

126. As mentioned, clozapine, the first atypical antipsychotic, was withdrawn from the market in 1975. Thus, the challenge was to find a clozapine-like molecule that produced the benefits of clozapine without the adverse side effects. Nichols Tr. 2743:14-2744:9; Paul Tr. 131:8-11; Schulz Tr. 3004:15-20.

127. The prior art confirmed that small structural changes in clozapine-like molecules led to unpredictable changes in properties. Changing the position of the chlorine atom in clozapine changed it from an atypical antipsychotic to a typical antipsychotic. TX 3465 at 878 ("[Clozapine's] 2-chloroisomer HF-2046 behaves like a classical neuroleptic. . ."); Nichols Tr. 2796:16-2797:3; LaVoie Tr. 1543:23-1544:11; LD 45; LD 94. Changing the ring structure of clozapine led to variable and unpredictable toxicities. Tilozepine caused seizures. TX 1356, compound 3; TX 1365 at col. 12, claim 12; TX 3772 at 394 (tilozapine (NT 104-252) clinical trials terminated); Nichols Tr. 2752:15-2754:11; LaVoie Tr. 1547:11-15, 1549:24-1551:3, 1552:115-19. Fluperlapine caused agranulocytosis in a some patients. TX 1356 at 809,

compound 2; TX 1387 at 155; Nichols Tr. 2745:18-2747:9, 2751:13-2752:14; LD 87. Removal of the halogen atom from clozapine and fluperlapine (yielding perlapine) destroyed antipsychotic activity. TX 1317 at 712, col. 2; TX 3124, compound 1c; Tupper Tr. 420:1-14; Nichols Tr. 2744:22-2745:17, 2747:10-2748:10; LaVoie Tr. 1545:8-18; LD 142; LD 143.

b. The '574 Patent

128. As noted, the '574 patent, issued on September 19, 1978, describes a family of chemical compounds of thieno[1, 5]benzodiazepines that have useful central nervous system ("CNS") activity. TX 3129 (abstract); Reith Tr. 848:10-15. The unique properties of these compounds render them particularly "useful in the treatment of mild anxiety states and certain kinds of psychotic conditions such as schizophrenia and acute mania." TX 3129, col. 13:62-66; Reith Tr. 853:12-20; Nichols Tr. 2839:19-2840:1.

129. The text of the '574 patent was written in 1975.

130. The first compound specifically mentioned in the '574 patent is ethyl flumezapine, which is the sole compound identified as "particularly active." The chemical name of that compound is 2-ethyl-7-fluoro-10-(4'-methyl-1'-piperazinyl)-4H-thieno[2,3-b][1,5]benzodiazepine. TX 3129, col. 4:30-34. Ethyl flumezapine has a fluorine atom on the benzene ring. This fluorinated compound is the only compound that

the '574 patent specification describes in actual examples of pharmaceutical formulations. TX 3129, Examples 37-40, col. 37, 1.62 — col. 39, 1.12; Tupper Tr. 431:20-432:22; Nichols Tr. 2749:5-9.

131. The specification identifies about one hundred other compounds as examples of the compounds of the invention, including flumezapine and compound '222. *See* TX 3129, col. 4-6, 15-37. No biological data is reported, however, for any of the compounds and no specific compound, other than ethyl flumezapine, is identified as being particularly active. TX 3129.

132. While the '574 patent claims unhalogenated compounds among the millions of compounds described in claim 1, the patent expresses a preference for halogen-containing compounds and specifically those with a halogenated substituent on the benzene ring in a location analogous to the chlorine in clozapine. TX 3129, col. 4:30-33, col. 39:42-62; Tupper Tr. 433:5-14; Nichols Tr. 2749:5-9.

133. In fact, the patent contains six claims defining specific compounds each containing a fluorine or a chlorine atom. Tupper Tr. 433:5-14; Nichols Tr. 2749:5-9; TX 3129, claims 2-7, col. 39:42-62.

134. Olanzapine is one of the millions of compounds within the scope of claim 1 of the '574 patent. TX 3129, col. 39:15-40; Reith Tr. 850:3-851:2; Hotten Dep. 160:10-22.

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c. The *Chakrabarti* Articles

135. The *Chakrabarti* publications also express a preference for halogen-containing compounds. *Chakrabarti 1980a*, previously discussed in Findings of Fact § IV.A.1, is also central to the obviousness inquiry.

(1) *Chakrabarti 1980a*

136. *Chakrabarti 1980a* reports on the *in vivo* behavior and toxicity testing of some individual compounds within the generic family of the thienobenzodiazepines. TX 3465.

137. The authors expressed a preference for a halogen substituent at the 7-position of the phenyl ring. Tupper Tr. 434:12-435:3; TX 3465 at 879; Finding of Fact # 109.

138. The five preferred compounds identified by the authors (compounds 9, 12, 17, 29, and 34) have CAR scores equal to or better than clozapine's score of three. Tupper Tr. 436:1-437:3; TX 3465 at 880-82. Compounds 9, 12, 17, and 29 have a fluorine at the 7-position, and compound 34 has a hydroxyethyl piperazine group on the piperazine ring. TX 3465; Nichols Tr. 2780:6-18; Findings of Fact # # 105, 107.

139. The authors also report that "[a] short alkyl substitution ([methyl, ethyl, isopropyl]) at position 2 of the thiophene ring seems to increase the activity."

TX 3465 at 879, col. 2. The authors compare the effect of a short alkyl substitution at position 2 versus a t-butyl substitution, a 2-hydrogen substitution, or other higher alkyl substitution. TX 3465 at 879, col. 2; Tupper Tr. 486:2-25. The only series of data that allows for each of these comparisons is based on results from fluorinated compounds. Tupper Tr. 435:10-25.

(2) *Chakrabarti 1982*

140. In *Chakrabarti 1982* the authors further confirmed the belief that neuroleptic substituents, such as fluorine atoms, were necessary for good antipsychotic activity. Each of the twelve thienobenzodiazepines described contains a fluorine atom at the 7-position. Reith Tr. 916:2-16; Nichols Tr. 2749:18-24; TX 3131 at 1135. The article specifically identifies fluorinated compounds "2 and 9" (flumezapine and ethyl flumezapine) as having "potent . . . activity." TX 3131 at 1137; Nichols Tr. 2749:18-24.

(3) *Chakrabarti 1989*

141. In J. K. Chakrabarti et al., *Synthesis and Pharmacological Evaluation of a Series of 4-Piperazinylpyrazolo [3,4-b]-and-[4,3-b][1,5] benzodiazapines as Potential Anxiolytics*, J. MED. CHEM. 2573 (1989) ("*Chakrabarti 1989*"), the authors reflected the ultimate preference for a fluorine substitution in this class of molecules by reporting that the fluorinated compound flumezapine "was

chosen as a candidate for clinical trial." Reith Tr. 922:25-923:3; Nichols Tr. 2749:25-2750:3; TX 3132 at 2574.

d. The *Sullivan and Franklin* Article

142. Sullivan and Franklin, *In Vitro Thiomethylation*, DRUG METABOLISM, AND DISPOSITION 276 (1985) ("*Sullivan and Franklin*"), reports a study in which flumezapine was administered to dogs and rats. The study found that a methylthio metabolite arose from the metabolism of flumezapine in the test animals. Nichols Tr. 2774:20-2775:10, 2843:23-2844:3; TX 3161.

143. There is some toxicity associated with compounds that are metabolized via methylthio metabolites. TX 3161; Nichols Tr. 2844:8-13. *Sullivan and Franklin* does not teach that the methylthio metabolic product is toxic. Reith Tr. 928:13-16; Nichols Tr. 2775:12-18. In addition, the article does not specifically state that flumezapine is toxic. Reith Tr. 927:9-11; Nichols Tr. 2775:11-13.

144. The article describes that during the metabolism of flumezapine, the fluorine at the 7-position is replaced by a methylthio group. Thus, one with ordinary skill in the art may have been motivated, based on the resulting potential toxicity from the metabolic process as described in the article, to consider developing a compound without the fluorine atom. Reith Tr. 858:22-859:6. There is, however, nothing in the article

to suggest that a hydrogen atom in place of the fluorine atom at the 7-position (yielding olanzapine) would be desirable, Nichols Tr. 2776:5-11, or that to make such a substitution would avoid the formation of the methylthio metabolite. Reith Tr. 929:11-18.

145. The article does not teach that replacing the fluorine with a hydrogen would stop the formation of the methylthio metabolite. Indeed, acetaminophen (Tylenol(R)), a non-fluorinated compound, also forms a methylthio metabolite. Reith Tr. 928:17-928:21; Nichols Tr. 2776:5-11.

2. Ordinary Skill in the Art

146. A person of ordinary skill in the art in this case would be a scientist with a Ph.D. in medicinal chemistry, pharmacology, or a similar discipline. Reith Tr. 819:23-820:6; Nichols 2850:25-2851:4; LaVoie 1527:22-1528:1.

147. Lilly's expert, Dr. David Nichols ("Dr. Nichols"), is personally familiar with the search for a safe, atypical antipsychotic, the relevant scope and content of the prior art, and the capabilities of a person of ordinary skill in the art. The court qualified him as an expert in medicinal chemistry. Nichols Tr. 2737:13-14.

148. Dr. Nichols obtained a Ph.D. in medicinal chemistry from the University of Iowa in 1973. Nichols Tr. 2733:25-2734:2; TX 3764.1. Dr. Nichols worked in the 1980s on developing antipsychotic compounds with an atypical activity profile; that is, active

antipsychotics, but with few side effects. Nichols Tr. 2735:13-2736:17. Dr. Nichols has taught the subject of antipsychotics for many years, including during the time period of the prior art at issue in this case. Nichols Tr. 2734:8-21. Dr. Nichols also has personal experience with the behavioral tests and other screening tests relied upon in *Chakrabarti 1980a*. Nichols Tr. 2735:25-2736:7. The focus of Dr. Nichols' research, however, has been hallucinogens and dopamine receptors. Nichols Tr. 2812:24-2813:6.

149. The court qualified Zenith's expert, Dr. Maarten Reith ("Dr. Reith"), as an expert in the field of molecular pharmacology and neuropharmacology. Reith Tr. 815:25-816:16. Dr. Reith has extensive experience with respect to dopamine and serotonin receptors, TX 3170, the specific areas of the brain at which the effects of antipsychotics are observed. TX 1000, col. 2:45-57; col. 7:6-59. Further, Dr. Reith demonstrated substantial knowledge of the tests used in *Chakrabarti 1980a*, as well as those reported in the declarations of Lilly's scientists. *See e.g.*, Reith Tr. 821:16-827:17, 865:1-866:24.

3. The Differences Between the Claimed Invention and the Prior Art

150. Structurally, olanzapine differs from clozapine in that olanzapine has a methyl-substituted thiophene ring in place of the benzene ring in clozapine. Olanzapine also has a hydrogen in place of the chlorine on its benzene ring. *See e.g.*, LD 52; LD 80. Clozapine caused agranulocytosis in humans. Paul Tr. 117:3-24.

151. Olanzapine differs structurally from ethyl flumezapine by replacement of the fluorine and ethyl group in ethyl flumezapine with a hydrogen and methyl group respectively. *See e.g.*, LD 48; LD 52. Ethyl flumezapine caused widespread blood problems in dogs; olanzapine did not. Nichols Tr. 2798:4-2800:25.

152. Olanzapine differs structurally from flumezapine, described as the lone clinical trial candidate out of this series of compounds, by substituting a hydrogen atom for the fluorine atom in flumezapine at the 7-position of the benzene ring. *See e.g.*, LD 49; LD 52; Nichols Tr. 2801:1-2802:11.

153. Olanzapine differs structurally from its ethyl analog, compound '222, by replacement of the ethyl group with a methyl group at the 2-position of the thiophene ring. *See e.g.*, LD 50; LD 52. In Lilly's D07290 Study, compound 222 caused a significant increase in cholesterol in female beagle dogs; olanzapine did not. TX 1001.1 at FH 149-54; McGrath Dep. 85:13-89:12.

4. Motivation Provided By the Prior Art to Make Olanzapine

a. Compound 222 as the Beginning Compound

154. The 574 patent specifically names over one hundred compounds, including compound '222. TX 3129, col. 4-6, 15-37, Example 26(a). The patentees did not

differentiate compound '222 from the other exemplary compounds in the way that they did with ethyl flumezapine. TX 3129, col. 4:30-34.

155. Compound '222 is not halogenated and, therefore, does not satisfy the preference expressed in the 574 patent itself, in *Chakrabarti 1980a*, *Chakrabarti 1982*, or *Chakrabarti 1989*. Nichols Tr. 2748:11-2750:9, 1772:18-1773:2; Reith Tr. 898:12-899:10, 914:7-915:4, 916:2-16, 922:9-923:3; LaVoie Tr. 1566:5-12.

(1) Compound '222's Activity

156. *Chakrabarti 1980a* did not provide specific motivation to use compound '222 as a starting point for further research. In fact, the article reported that compound '222, corresponding to compound 6 in Table I, did not have the minimum CAR score of three required for a suitable atypical antipsychotic agent and thus was not considered a preferred compound. Pullar Tr. 227:1-22; LaVoie Tr. 1568:11-1569:3;TX 3465 at 880-82.

(2) Hydrogen as a Preferred Substituent

157. *Chakrabarti 1980a* also did not provide specific motivation to substitute a hydrogen in the 7-position. One skilled in the art would not have recognized from compounds 6, 34, and 36 in *Chakrabarti 1980a* that a hydrogen in the 7-position was a desirable substituent.

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(a) Compound 6

158. *Chakrabarti 1980a* reported that compound 6 had a CAR score of two at 10 mg/kg. LaVoie Tr. 1568:11-1569:3; Pullar Tr. 227:1-22; Tupper Tr. 437:22-438:2; Nichols Tr. 2772:18-2773:2; TX 3465 at 880-81.

159. A better CAR score for compound 6 could not be achieved by increasing the dose, since higher doses would cause the test animal to completely stop responding to the test stimuli due to muscular incoordination. Pullar Tr. 223:8-224:2. Dr. Pullar explained that increasing the dose caused the test animals to completely stop responding to the test — a distinctly negative outcome. These results, based on tests with the compound administered orally, were corroborated with other results using intraperitoneal (IP) administration. Increasing the dose in both cases could not increase the activity of compound 6 above the substandard CAR score of two. Pullar Tr. 224:18-228:3; TX 3470.

160. The evidence does not support the argument that a person of ordinary skill in the art would presume that compound 6's corresponding free base (compound '222) would be more active. The difference between a maleate salt and a free base is just their physical forms, with salts typically being used for ease of handling. It is the same molecule in both forms. Tupper Tr. 504:20-505:8. As Dr. Tupper explained, the form (salt or free base) does not fundamentally change the pharmacological action. Tupper Tr. 505:5-

8. There are some differences in the way the body processes the salt of a compound versus its free base due to the varying size of the particles. But if administered to achieve equal concentrations in the blood, the free base and maleate salt should produce the same results, and one would expect the same activity between the two forms. Nichols Tr. 2883:10-16; Tupper Tr. 505:11-17. Indeed, prior to trial, Dr. Reith made no distinction between compound 6 and its free base (compound 222) and actually treated them interchangeably. Reith Tr. 909:8-20.

161. Accordingly, one of ordinary skill in the art would not have understood from a close reading of *Chakrabarti 1980a* that compound 6 was a preferred compound, and hence, that a hydrogen in the 7-position would have been preferred.

(b) Compound 36

162. *Chakrabarti 1980a* reported that compounds 34, 35, and 36 "retained good activity." TX 3465 at 879, col. 2 ("However, compounds (34-36) . . . retain good activity."). The statement regarding the activity of compounds 34-36 was made in the context of comparing the compounds, in which each had a hydroxyethyl or hydroxypropyl on the piperazine ring (and which had good activity), to compounds 31-33 having other substituents on that ring (and which were less active or inactive). Nichols Tr. 2830:18-2831:14; TX 3465 at 879.

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163. Compound 36 received a CAR score of two at a dose of 10 mg/kg, and a CAT score of two at a dose of 12.5 mg/kg. As stated previously, a CAR score of two was not preferred. Pullar Tr. 227:1-22, 255:12-256:13.

164. Dr. Tupper testified that because of the manner in which the test was scored, a reported CAR score of two encompassed a broad range of activity ranging from a 31% to 50% block of the conditioned avoidance response. Pullar Tr. 229:12-230:14; TX 3465 at 882 n.d. Only the authors knew where in that score range each compound fell, and there is no way for the reader to second guess the judgment of the authors as to which compounds were "good" and which were not. Pullar Tr. 294:15-24; Nichols Tr. 2778:12-22; LaVoie Tr. 1561:17-25.

165. Therefore, the fact that the authors stated that compound 36 "retained good activity" with a CAR score of two can at most be interpreted as a reference to a compound at the high end of the "two" range approaching a 50% block. It cannot be taken as a statement that all compounds with a reported CAR score of two (with activities as low as 31%) were good, active compounds when the remaining text of the article indicated that they were not.

166. One of ordinary skill in the art would not have understood from a reading of *Chakrabarti 1980a* that compound 36 was a preferred compound. The fact that the authors' stated that compound 36 "retained good activity," read in its proper context, is not evidence to the contrary.

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(c) Compound 34

167. Compound 34 is singled out by the authors as a preferred compound. TX 3465. This compound, like olanzapine, has a hydrogen substituent at the R1 or 7-position, but, unlike olanzapine, also has a hydroxyethyl piperazine group on the piperazine ring. Such hydroxyethyl piperazine groups were known to enhance the activity of antipsychotic drugs. LaVoie Tr. 1564:24-1565:4, 1567:11-22; Nichols Tr. 2779:25-2786:22 ("There was a recognition in the art that a hydroxyethyl had special properties . . . In general, the compounds were more potent. They usually had better brain penetration. . .").

168. The identification of five preferred compounds by *Chakrabarti 1980a*, each of which had either a fluorine or a hyroxyethyl piperazine substituent, could not rationally be read by a person actually skilled in this field to be an expression of preference for compounds like olanzapine that have neither a fluorine atom nor a hydroxyethyl piperazine group. Nichols Tr. 2786:12-2788:8; Reith Tr. 901:15-902:8.

169. Nothing in *Chakrabarti 1980a* provides motivation for a person with ordinary skill in the art to begin with compound '222 over one of the compounds the authors endorse as preferred. Nichols Tr. 2272:22-23, 2273:1-12.

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b. Changing the 2-methyl in Compound '222 to a 2-ethyl

170. One skilled in the art would not have been motivated to modify compound '222 by changing the ethyl group to a methyl group at the 2-position of the thiophene ring because there is no suggestion in the '574 patent or any other prior art that such a modification would have increased activity and decreased unwanted side effects. Reith Tr. 915:20-916:1; LaVoie Tr. 1562:1-6; Nichols Tr. 2772:18-2774:7. Even if a person of ordinary skill in the art were motivated to begin with compound 222, he would modify it by adding a halogen atom to give it the neuroleptic substituent believed at the time to be required for antipsychotic activity. Nichols Tr. 2773:13-19.

171. Although *Chakrabarti 1980a* reports that "[a] short alkyl substitution ([methyl, ethyl, isopropyl]) at position 2 of the thiophene ring seems to increase the activity," TX 3465 at 879, col. 2, the article does not state that any particular short alkyl group will provide better results than any other short alkyl group. Reith Tr. 915:20-916:1; LaVoie Tr. 1574:2-4; Nichols Tr. 2273:20-2274:7.

172. The only compounds for which data is given allowing comparison of hydrogen at the 2-position with all of the "short alkyl" substitutions at the 2-position (as well as the longer alkyls, e.g., "bulky t-Bu group") as described in the text are compounds 8 through 21 — all of which have a fluorine at the 7-position of the

benzene ring. Tupper Tr. 435:20-25; Reith Tr. 915:5-19; LaVoie Tr. 1574:2-9; TX 3465 at 880-81. Compounds 6 and 7, neither of which is identified as preferred, provide an isolated example of a comparison between a short alkyl substitution and a t-butyl substitution in unfluorinated compounds. Tupper Tr. 487:1-7.

173. Regardless of this one comparison, the paragraph in *Chakrabarti 1980a* in which this preferred substituent is revealed states a preference for short alkyl groups in the context of a fluorinated series of compounds; thus the article does not generally provide motivation or guidance relating to the effect of such substitution on fundamentally different unfluorinated molecules. Reith Tr. 915:5-19; Nichols Tr. 2772:18-2774:7.

c. Replacing the Fluorine Atom in Flumezapine with a Hydrogen Atom

174. Defendants contend that one of ordinary skill in the art would have been motivated to replace the fluorine atom in flumezapine with a hydrogen atom in the 7-position of the benzene ring to arrive at olanzapine.

175. In light of the general state of the art, including the teachings of the '574 patent and *Chakrabarti 1980a*, *Chakrabarti 1982*, and *Chakrabarti 1989*, one of ordinary skill in the art would have expected that replacing the fluorine atom with a hydrogen atom would produce a compound without sufficient antipsychotic activity. Nichols Tr. 2776:5-11.

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176. While *Chakrabarti 1980a* suggests that a chlorine atom in place of the fluorine atom would also enhance the compound's activity, it does not specifically suggest that the same result could be obtained with a hydrogen atom. Nichols Tr. 2779:17-24; TX 3465 at 879, col. 2. Nor does anything in *Sullivan and Franklin* suggest the desirability of using a hydrogen atom at this position. Nichols 2776:5-11; TX 3161; Findings of Fact § IV.B.1.d. If one were looking to replace the fluorine, one would replace the fluorine with other electronegative groups, not hydrogen. TX 1315 at 3172; LaVoie Tr. 1572:12-1573:18. Indeed, the art as a whole teaches directly away from using hydrogen because it is not an electron-withdrawing substituent. Nichols Tr. 2773:3-12.

177. Moreover, the 1990 publication, Davis et al., *Chloro-Substituted, Sterically Hindered 5,11 Dicarbo Analogues of Clozapine as Potential Chiral Antipsychotic Agents*, J. MED. CHEM, 809 (1990), proposed that the possible toxicity of candidates that were being investigated as safe alternatives to clozapine (including flumezapine) might be due to the presence of so-called "hetero atoms" — nitrogens and sulfurs — in the three-ring system of those compounds. Nichols Tr. 2757:21-2758:10; TX 1356 at 809. Those hetero atoms have nothing to do with the fluorine atom, and if those hetero atoms were removed, one would not obtain olanzapine. Nichols Tr. 2757:21-2758:16; TX 1356.

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5. Reasonable Expectation of Success

178. By April 1990, a person with ordinary skill in the art knew facts that would have foreclosed a reasonable expectation of success with other clozapine-like compounds. These include: (1) the first known atypical antipsychotic drug, clozapine, was known to interact with a large number of receptors in the brain, including dopamine receptors, serotonin receptors, and cholinergic receptors, Paul Tr. 121:20-122:8, LaVoie Tr. 1541:24-1542:8, Nichols Tr. 2763:6-2765:10; (2) it was not known through what combination of these or other receptors clozapine exerted its atypical antipsychotic action, Nichols Tr. 2763:6-16; (3) it was not known why clozapine caused agranulocytosis in humans, Paul Tr. 121:14-17, Nichols Tr. 2769:13-17; (4) many compounds identified in patents and publications during the 1970s and 1980s as potential antipsychotic drugs had failed in clinical trials due to lack of efficacy, lack of atypicality, and/or an array of adverse side effects, Nichols Tr. 2751:1-2757:14; TX 1356; (5) small structural changes in clozapine-like molecules yielded great and unpredictable changes in properties, Pentel Tr. 1926:25-1927:9; Nichols Tr. 2796:6-2804:14; and (6) many researchers made a large number of compounds over a long period of time in an effort to find a safe, atypical antipsychotic drug and failed. Nichols Tr. 2743:14-2744:17, 2751:1-4; TX 1397 at ZY 19 66.

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179. In 1990, a skilled artisan would have believed that a halogen atom on clozapine was important for its antipsychotic activity, that the particularly active members of the thienobenzodiazepine family had a halogen, and that the only member of that family of compounds to be advanced to clinical trials, flumezapine, had a halogen atom. Nichols Tr. 2748:11-2750:9, 2772:18-2773:2; Reith Tr. 916:2-16; LaVoie Tr. 1566:5-12; TX 3129; TX 3131; TX 3132; TX 3465. A person of ordinary skill in the art would not likely assume that the halogen substituent widely used on this class of compounds could be eliminated without adverse effect. Nichols Tr. 2774:8-19.

180. In 1990, a skilled artisan would not have reasonably expected, based on the data from the animal tests, that any of the compounds identified in *Chakrabarti 1980a* would be effective antipsychotics. The animal behavioral tests reported in *Chakrabarti 1980a* were only indicators of *potential* antipsychotic activity. Reith Tr. 929:22-930:17; Nichols Tr. 2768:16-2769:11.

181. Moreover, these animal tests were not indicative of a compound being a safe, atypical antipsychotic, which was the goal of researchers after the toxicity of clozapine was recognized in patients. Pullar Tr. 173:21-174:12; TX 1031 at ZYP 506 1725; Reith Tr. 930:5-932:12; Nichols Tr. 2768:16-2769:24; Tupper Tr. 457:20-458:2. Indeed, the two most preferred compounds identified as showing good activity in the *Chakrabarti* prior art, flumezapine and ethyl

flumezapine, turned out to be toxic. Pullar Tr. 180:2-181:8, 188:13-189:14. Thus, there would have been no reasonable basis from *Chakrabarti 1980a* to expect that new compounds such as olanzapine would have been safe, atypical antipsychotics.

182. In light of these facts, at the time olanzapine was developed, there could have been no reasonable expectation of success that an unhalogenated compound structurally similar to compound '222 would succeed as a safe and effective atypical antipsychotic.

6. Composition and Method Claims

183. Claims 2, 3, 7, 8, and 15 are the composition and method claims of the '382 patent. TX 1000.

a. Claim 1 claims the compound olanzapine. TX 1000, col. 12.

b. Claims 2, 3, and 15 claim "pharmaceutical compositions" of the compound claimed in claim 1. TX 1000, col. 12.

c. Claim 7 claims a method for treating an animal suffering from or susceptible to schizophrenia using the compound claimed in claim 1. TX 1000, col. 12.

d. Claim 8 claims "[a] method of claim 7 wherein the effective amount is from 0.1 to 20 mg per day" of the compound claimed in claim 1. TX 1000, col. 12.

184. The '574 patent, the *Chakrabarti* publications, and the *Sullivan and Franklin* article do not teach or suggest either the use of olanzapine in amounts less than 20 mg/day to treat schizophrenia or the dosage forms for such treatment. Dr. Reith and Dr. LaVoie did not offer any trial testimony that the references teach or suggest what an "effective amount" of olanzapine would be to treat a human suffering from or susceptible to schizophrenia. Dr. Reith agreed that the '574 patent refers to doses in the range of 0.1 to 20 mg/kg/day, equivalent to between 7 and 1400 mg/day for a 70 kilogram (150 pound) person, and that the '574 patent provides no guidance as to where in that range one should treat an actual schizophrenic patient with olanzapine. Reith Tr. 905:8-906:3. Similarly, Dr. LaVoie conceded on cross-examination that the '574 patent referred to 0.1 to 20 mg/kg/day while the '382 patent referred to 0.1 to 20 mg/day, a 70-fold difference for a 70 kilogram (150 pound) person. LaVoie Tr. 1574:23-1575:9.

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7. Secondary Considerations

a. Long-Felt Need

185. Beginning at least as early as 1975, there was a long-felt need for a safe, atypical antipsychotic drug that remained unsatisfied at the time Lilly filed the olanzapine patent application in 1990. Nichols Tr. 2751:1-4, 2808:5; Schultz Tr. 2971:8-2972:17; TX 1397 at ZY 19 66 ("The medical need for better antipsychotic drugs in terms of increased efficacy and fewer unwanted effects is great").

186. Numerous investigators, including scientists at Lilly, tried but failed to develop a safe, atypical antipsychotic drug between 1975 and 1990. Nichols Tr. 2751:1-12; Schulz Tr. 2971:8-2972:17; TX 1356; TX 1397 at ZY 19 46-48, 54-58, 66.

187. Risperidone (marketed and sold by Jansen Pharmaceuticals as Risperdal) is an atypical antipsychotic. It was first prescribed to schizophrenic patients in February 1994. Olanzapine (marketed as Zyprexa) was first prescribed in October 1996. Schulz Tr. 2987:15-17, 2988: 15-17; Kinon Tr. 2526:24-2527:2; TX 1590; LD 113.

188. Risperidone and olanzapine are prescribed by doctors more than any other atypical antipsychotic on the market. *See* TX 1590. Risperidone, however, is prescribed more often than olanzapine. TX 1590 at

ZYP 528 16; LD 113; Paul Tr. 150:13-151:2; *see also* Finding of Fact # 193.

189. There is no evidence in the record to establish when the risperidone patent application was filed.

190. Because risperidone was not prescribed or otherwise available to schizophrenic patients at the time the '382 patent was filed, olanzapine met the long-felt but unsolved need for a safe, atypical antipsychotic.

b. Failure of Others

191. As reflected in the court's previous findings, there was a failure by others to develop a safe, atypical antipsychotic drug prior to the filing of the olanzapine patent application in the U.K. *See* Findings of Fact § II.D.

c. Commercial Success

192. Since late 1996, when olanzapine was approved for use, it has captured significant market share in terms of the number of prescriptions written for antipsychotic medications. TX 1590.

193. In 2001, olanzapine accounted for more than 25% of all antipsychotic prescriptions written, and risperidone accounted for more than 29% of all antipsychotic prescriptions written. TX 1590.

194. In 2001, olanzapines' U.S. sales were $ 2.18 billion, representing one third of Lilly's revenues for that year. TX 1597; Paul Tr. 139:6-8.

195. Lilly also spent a substantial portion of its revenue on marketing and administrative costs. Between 1996-2001, Lilly spent more on marketing and administrative costs than on research and development. Paul Tr. 148:5-149:3.

196. The evidence of the commercial success of olanzapine does not weigh in favor of either Lilly or the Defendants.

d. Industry Acclaim

197. Olanzapine has received substantial industry acclaim in the form of the Prix Galien Award in 1997, and Queens Award for Enterprise in 2000, and the Pharmaceutical Manufacturer's Association Discoverer's Award in 2000. In addition, testimonials from treating doctors and patients provide objective evidence of olanzapine's nonobviousness. Trial Tr. 2730:12-2731:15 (stating the February 10, 2004 Stipulation regarding awards received for the discovery of olanzapine); Paul Tr. 142:4-143:8; Schulz Tr. 2973: 10-2974:2.

198. Although the inventor of risperidone received the Prix Galien Award in 1996, Trial Tr. 2730:24-25, that fact does not vitiate the industry acclaim held by olanzapine.

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e. Unexpected Differences Between Compound 222 and Olanzapine — The Dog Studies

(1) Basic Principles of Toxicology

199. Drug development relies heavily on animal testing to try to find drugs that will be safe for human use. Testing first directly on human subjects was, and still is, unethical and unheard of in modern drug development. Instead, testing in animals always precedes human clinical studies. The genetic make-up, organ systems, and biochemistry in other mammals are sufficiently similar to those in humans that one can study adverse effects of drugs in laboratory animals. Dr. Shayne Gad ("Dr. Gad"), Zenith's expert in toxicology, testified, "it is a fundamental hypothesis of toxicology that adverse effects caused by chemical entities in animals are generally the same as those induced by those entities in humans . . ." Gad Tr. 1753:9-13. Thus, the field of toxicology relates generally to the testing of drugs in animals in an effort to identify toxic risks for humans. Emmerson Tr. 512:17-20; Gad Tr. 1754:1-12.

200. Toxicity testing is done in order to identify the potential toxic effects of drug candidates under development. Gad Tr. 1754:1-6, 1756:1-12. Such testing is done at doses chosen to elicit any toxic effects, that is, at or near the "maximum tolerated dose" or "MTD." Maximum tolerated dose means the highest dose an animal can receive consistent with

living and general good health. Emmerson Tr. 539:4-8. The MTD and fractions thereof are appropriate doses for pharmaceutical toxicology testing so that the full range of potential toxicities can be observed. Emmerson Tr. 539:10-14; Kanter Tr. 2102:9-2103:4. Indeed, if a compound is not tested at or near the MTD, an "important adverse finding that is attributed to treatment with the compound" can be missed. Emmerson Tr. 539:22-25. This is because humans are generally more sensitive to the toxic effects of drugs than a homogeneous population of laboratory animals. Emmerson Tr. 526:4-13, 539:15-25.

(2) Lilly's and Defendants' Dog Toxicology Studies

(a) Lilly's D07290 Dog Study

201. The D07290 Dog Study was a toxicology study conducted by Lilly at the request of Lilly's patent department. Emmerson Tr. 568:3-7.

202. The D07290 Dog Study compared five groups of beagle dogs: a control group that received a placebo, a group that received 4/mg/kg/day of olanzapine, a group that received 4 mg/kg/day of compound '222, a group that received 8 mg/kg/day of olanzapine, and a group that received 8 mg/kg/day of compound '222. Each group consisted of eight dogs, four males and four females. TX 1164 at ZY 622 340.

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203. Drug administration to dogs commenced on September 25, 1990, and ended on April 2, 1991. TX 1164 at ZY 622 340.

204. At the conclusion of the D07290 Study, Lilly claimed that the four females in the high-dose compound '222 group showed a statistically significant increase in group average (mean) cholesterol over time as compared to female control animals and the high-dose female dogs given olanzapine. *See* TX 1001.1 at FH 150-51, 154.

(b) Zenith's Dog Study — The MPI Study

205. Zenith commissioned a dog toxicology study, which was conducted at MPI Research, Inc. ("MPI"), for purposes of this litigation (the "MPI Study" or "Zenith Study"). The Zenith Study, like the Lilly Study, lasted six months. Drug administration to dogs lasted from May 3, 2002, to November 4, 2002. TX 1188 at ZG 001604.

206. The Zenith Study was an expanded comparison of olanzapine and compound '222 in female beagle dogs at a dose of 8 mg/kg/day. TX 1188 at ZG 001608. Included in the Zenith Study were measurements of progesterone in order to evaluate the estrous state of the female dogs. TX 1188 at ZG 001613. Zenith's Study design thus allowed consideration of the estrous cycle in individual animals and permitted study of the possible effect of the drug on that cycle as well as

the relation of that cycle to the levels of cholesterol that were observed. Nachreiner Tr. 1099:6-25. The Zenith Study was conducted according to GLP guidelines. TX 1188 at ZG 001603.

207. In the Zenith Study, there were fifteen female dogs assigned to each of three groups. Group 1 was a nontreated control group. Group 2 was a group in which each dog was given 8 mg/kg/day of '222. Group 3 was a group in which each dog was given 8 mg/kg/day of olanzapine. TX 1188 at ZG 001608. The dogs were assigned to the groups based on body weight and cholesterol levels, but not based on pretest estrous state. TX 1188 at ZG 001606. Blood samples for cholesterol analysis were taken before the test began, twice within the first week after dosing started, and then at monthly intervals. TX 1188 at ZG 1611-12.

208. Before administering the test compounds, Zenith divided the dogs into three test groups that all had the same average cholesterol level, excluding in the process any dog with a cholesterol level above 175 mg/dl. Nachreiner Tr. 1111:2-6; Goldenthal Dep. 131:8-15. The dogs in the Lilly D07290 Study were not preselected to have cholesterol levels under 175 mg/dl. Nachreiner Tr. 1111:7-9. The difference between the average cholesterol values of the untreated dogs in the Zenith Study and the untreated dogs in Lilly's D07290 Study was approximately 40 mg/dl. Nachreiner Tr. 1112:8-11.

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209. The numerical magnitude of the increase in cholesterol caused by compound 222 in both the D07290 and Zenith Studies was about 40 mg/dl. Thisted Tr. 3108:5-3109:6. When the effect of progesterone (estrus) is filtered out, the magnitude of the estimated difference is about the same, i.e., about 40 mg/dl. Thisted Tr. 3093:25-3095:3; Gibbons Tr. 2221:10-22, 2269:8-11. The numerical difference in mean cholesterol levels, 40 mg/dl, and the fact that the mean cholesterol was shifted upward by one standard deviation, are both good measures of effect magnitude. Thisted Tr. 3122:3-9.

210. The Zenith Study also purported to measure the fractions of total cholesterol carried as HDL and LDL. Beginning with the week two bleeding, and at every subsequent time point, the mean LDL cholesterol values for the compound '222-treated dogs were statistically significantly higher than those for the olanzapine-treated dogs and the control dogs. Nachreiner Tr. 1118:12-1119:3; Goldenthal Dep. 265:1-11. Over the course of six months, the compound 222-treated dogs experienced an 18 point increase in HDL and a 22.6 point increase in LDL. Scanu Tr. 1277:13-1279:6, 1309:12-14. In these dogs, the percentage of LDL increased six times more than the percentage of HDL. Scanu Tr. 1309:5-11.

211. In short, the results of Zenith's MPI Study confirmed the findings of the D07290 Study that cholesterol in the female high-dose compound '222 group was significantly greater than in the olanzapine and control

groups, whereas the olanzapine group did not differ significantly from the control group.

(c) DRL's Dog Study — The Calvert Study

212. Unlike the Lilly and Zenith toxicology studies, the study commissioned by DRL and conducted by Calvert Preclinical Services, Inc. (the "Calvert Study") lasted only sixty days — from April 2, 2002, to July 2, 2002. Gayheart-Walsten Dep. 83:16-18; TX 1180 at DRL-IN 055560, 055563. The only clinical chemistry variable studied was cholesterol. TX 1180 at DRL-IN 055560. There were ten female beagle dogs in each of four groups: (1) a control group, (2) a group given 8 mg/kg/day of compound 222, (3) a group given 8 mg/kg/day of olanzapine, and (4) a group of untreated dogs that were offered double rations of food. The researchers gave the dogs in Group 4 double the normal ration of food to see if doing so would have an effect on cholesterol concentrations. TX 1180 at DRL-IN 055560, 055566-67.

213. While the Calvert Study is fundamentally too short to compare to the longer Lilly and Zenith Studies, Rebar Tr. 2318:22-2319:2, the observed effects on cholesterol are consistent with those in the longer studies. Thisted Tr. 3124:20-3126:9. For example, there was a rapid increase in cholesterol concentrations in the compound 222-treated group. Thisted Tr. 3125:24-25. The mean cholesterol values

in the compound '222-treated dogs were greater than in the olanzapine-treated dogs at all time points. Kanter Tr. 2162:22-2163:5; Gayheart-Walsten Dep. 102:5-17. In addition, the cholesterol levels of the control dogs rose over the course of the Calvert Study. Thisted Tr. 3126:1-3.

214. The cholesterol concentrations did not increase in the group of dogs offered double rations of food. Gayheart-Walsten Dep. 103:13-20, 104:8-105:12; Kanter Tr. 2160:16-18.

(3) Criticisms of Lilly's Dog Study Evidence

215. Defendants attack the D07290 Study on numerous grounds and assert that the data and the conclusions drawn therefrom by Lilly scientists are seriously confounded.

(a) The Dog as a Model

216. The dog is an appropriate species in which to test for potential toxic effects in humans, including effects on total cholesterol. Emmerson Tr. 525:4-18; *see, e.g.*, TX 1272; TX 1278; TX 3072 at DRL IN 055565; TX 3087.

217. By 1990, the beagle dog had emerged as the large mammal of choice for toxicology testing of new drug candidates. Emmerson Tr. 572:3-19; Means Tr. 1998:9-18. The dog, while not perfectly predictive,

is reasonably predictive of toxic effects in humans. Gad Tr. 1754:1-6; Kanter Tr. 2105:8-20, 2120:16-22; Means Tr. 1998:24-1999:7. A wealth of expert testimony and literature supports the finding that the dog is an acceptable toxicity model for humans. The writings of Zenith's expert toxicologist, Dr. Gad, teach "that the dog is currently the first choice nonrodent model for toxicity studies . . ." Gad Tr. 1758:1-4.

218. The dog model was widely used by Lilly in a variety of studies early in the development work leading to the discovery of olanzapine. These studies, conducted and reviewed over a period of years, provided the basis for making decisions to terminate or advance testing of drug candidates such as olanzapine. *See* Emmerson Tr. 542:6-21, 543:10-13, 545:17-546:5, 546:22-547:1.

(b) Total Cholesterol as a Tested Parameter

219. Over the years, a standard battery of observations and measurements seeking to detect the toxic effects of drugs in dogs has been developed. As technology and measurement methods improved, this standard battery grew. By 1990, the standard battery included measurement of total cholesterol. Gad Tr. 1758:5-13; TX 3107 at 121; Emmerson Tr. 536:16-23. The design of the D07290 Dog Study, therefore, included a measurement of total cholesterol as part of the then

standard battery of dog toxicology tests. Emmerson Tr. 535:16-536:25.

220. In this regard, the laboratory retained by DRL to conduct DRL's Calvert Study for this litigation reported that "the beagle dog is an acceptable species to study the effects of compounds and diet on total cholesterol, triglycerides, HDL, LDL, and VLDL." TX 3072 at 11. Similar conclusions have been drawn in the literature. A 1997 article in the journal *Atherosclerosis* states in reference to the beagle dog, "this animal model has been successfully used to demonstrate the effect of statins [cholesterol lowering drugs] on cholesterol . . ." and that "this animal model has good predictive power for hypocholesterolemic effects in man." TX 3087 at 203; Scanu Tr. 1286:20-1288:10; Davidson Tr. 2919:2-14.

221. Both dogs and humans can experience elevations in total cholesterol concentrations as the result of similar metabolic effects and abnormalities. Scanu Tr. 1260:11-1263:24; Gad Tr. 1810:16-22. Examples of hypercholesterolemias (elevation of serum cholesterol concentrations) in both dogs and humans with common etiologies include the ingestion of high-fat diets, cholestasis, hypothyroidism, diabetes mellitus, pancreatitis, hyperadrenocorticism, and nephrotic syndrome. Bauer Tr. 2665:23-2668:15; TX 1347.

222. There is a known and reported nexus between dog studies and humans with regard to total cholesterol. Dr. Michael Davidson ("Dr. Davidson"), Lilly's expert

in cardiology, cholesterol, and cardiovascular disease, Davidson Tr. 2891:13-14, 2897:25-2898:5, testified that he has been involved in human clinical trials for statin drugs, including Mevacor, Zocor, Pravacol, Lipitor, and Crestor. Davidson Tr. 2893:17-2894:5. Dr. Davidson testified that the experimental statins were tested in dogs before they were tested in people. Davidson Tr. 2919:2-21. Indeed, the dogs proved to be a reasonable predictor of cholesterol effects in humans in that statins decrease cholesterol in both dogs and humans. Davidson Tr. 2918:12-15, 2919:2-21. Moreover, there are a number of articles regarding statin research that show that the dog is used by large, established pharmaceutical companies as an appropriate model to indicate whether drugs may lower cholesterol in people. *See, e.g.*, Scanu Tr. 1286:20-1293:10; TX 1272, 1273, 1275, 1278, 3087. Dr. Davidson further testified that rapamycin, a.k.a. Rapamune, a drug that prevents transplant rejection in organ transplant patients, raised cholesterol in both dogs and humans. Davidson 2926:1-5, 2927:12-14 (humans), 2928:16 (dogs); *see also* Scanu 1253:18-25 (humans); TX 1353 (humans).

223. Dr. John Bauer ("Dr. Bauer"), Lilly's expert in lipids and lipoproteins in dogs as well as comparative studies in humans and dogs, Bauer Tr. 2655:10-12, testified that "observations of total blood cholesterol or total serum cholesterol [in dogs] using the terms equally are a useful predictive index for the response of total blood cholesterol in humans." Bauer Tr. 2655:15-2659:4. This opinion is implicit in many of

his writings and is explicitly stated in an article he wrote in 1996. Bauer Tr. 2655:25-2657:16; TX 1347. Dr. Bauer summarized three reasons for his opinion that dogs are good models to predict cholesterol effects in humans: (1) the many similarities in cholesterol metabolism in humans and dogs; (2) the similar effects in cholesterol in humans and dogs caused by diseases; and (3) the considerable literature on the effects of experimental compounds on cholesterol in dogs and humans, showing that cholesterol reductions or elevations seen in dogs were also seen in humans. Bauer Tr. 2658:2-2659:4.

224. There are recognized differences in the way cholesterol is metabolized in dogs and humans. Humans carry most of their cholesterol in LDL, the so-called "bad cholesterol," while dogs carry most of their cholesterol in HDL, the so-called "good cholesterol." Scanu Tr. 1210:6-17; Bauer Tr. 2708:18-22. Consequently, when total cholesterol is elevated in dogs, the resulting increase in HDL cholesterol does not usually form atherosclerotic plaque in dogs. In contrast, when total cholesterol is elevated in humans, it is carried primarily as LDL, thereby increasing atherogenic risk in humans. Bauer Tr. 2667:5-12, 2721:5-12.

225. Because dogs are resistant to elevated cholesterol while humans are not, Dr. Bauer opined that if an experimental compound elevated cholesterol levels in dogs, then he would expect either an equal or greater increase in humans. Bauer Tr. 2675:13-

2676:17, 2678:4-7, 2678:18-2679:12. His opinion, although not supported by a published study or subjected to peer review, was based on his extensive experience studying comparative hypercholesterolemia in both species. Bauer Tr. 2703:15-2704:25. Thus, Dr. Bauer's expression of this untested theory does not diminish his credibility as a witness in his area of expertise — lipids and lipoproteins in dogs and comparative studies in humans and dogs.

226. One of the articles which Dr. Bauer cited in his expert report is an article entitled "SR-12813 lowers plasma cholesterol in beagle dogs by decreasing cholesterol biosynthesis." TX 3087. That article reports that the mechanism by which a statin drug works and the metabolic pathway through which it proceeds is known in both dogs and humans. TX 3087; Bauer 2694:12-2695:23. The mechanism by which a dog's cholesterol is raised is unknown. Bauer Tr. 2698:1-5. Despite this fact, this article remains consistent with the fact that there are similarities between the cholesterol metabolism in dogs and humans which render the dog a good predictive model for humans.

227. Dr. Bauer's opinion is supported by a chapter he co-wrote in *The Clinical Chemistry of Laboratory Animals*, TX 3779, which concluded that dogs remain a good model for predicting total cholesterol effects in humans. Bauer Tr. 2652:3-2654:3, 2656: 25-2657:16.

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228. Dr. Angelo Scanu ("Dr. Scanu"), Zenith's expert in lipoproteins, testified that in his experience in lipoprotein metabolism, his review of the D07290 Study, and his review of published literature in the area of lipoprotein metabolism, the dog is not a good animal model for predicting cholesterol results in human patients. The principle reason cited for his opinion is the fact that cholesterol is metabolized in a strikingly different manner in dogs as opposed to humans. Scanu Tr. 1200:14-1201:2.

229. Contrary to Dr. Scanu's opinion, the evidence demonstrates that this metabolic difference does not prevent the dog from being a good model for predicting total cholesterol results in humans. Bauer Tr. 2655:15-2659:4. Although differences exist between humans and dogs as to the manner in which total cholesterol elevations are metabolically transferred and disposed of, these differences are "downstream" from the causes of cholesterol elevations and, therefore, secondary to them. Bauer Tr. 2659:5-2665:18. For example, when dogs are fed high-fat diets, the hypercholesterolemic response in dogs is to partition excess cholesterol into HDL fractions, whereas humans partition the excess cholesterol into LDL fractions. Scanu Tr. 1273:11-1274:16. In either event, however, both dogs and humans experience an elevation in total cholesterol. Bauer Tr. 2676:18-2679:14; *see also* Finding of Fact # 221.

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(c) Randomization

230. In a well-designed experiment, animals are randomly assigned to treatment groups to remove systematic effects (aside from the treatment being studied), known and unknown, that could affect the outcomes being measured. A purpose of randomization is to ensure that subjective judgments play no role in which animals are assigned to which treatment groups. This eliminates a source of bias that otherwise could systematically favor one treatment group over others for reasons unrelated to the treatment itself. Thisted Tr. 3082:15-3083:1.

231. Lilly's design of a dog study using forty dogs randomly assigned by body weight is common in standard toxicology studies, and consistent with Lilly's standard operating procedure. Emmerson Tr. 571:22-572:2; Gad Tr. 1765:15-21; Gayheart-Walsten Dep. 127:7-128:9. There are a variety of physiological variations that might exist among dogs. The general purpose of random assignment based on body weight of dogs amongst the treatment groups is to balance out whatever variations may exist. Gad Tr. 1765:18-21, 1766:6-9.

232. At the start of the D07290 Study, there was one dog in the compound '222 group that weighed more than the others. The dog was not obese, and her weight was within the protocol guidelines. There is no evidence that the size of a dog affects its cholesterol

levels. Rebar Tr. 2333:3-21; TX 1164 at ZY 622 607 (body weight 5-12 kg), 688-97.

233. There was no reason that the dogs in the D07290 Study should have been randomized based on their estrous stage because (1) it was not common practice to examine female dogs for their estrous stage prior to standard toxicology tests, *see, e.g.*, Goldenthal Dep. 164:7-9 (stating that MPI has never randomized by estrous state prior to a study); (2) it was a common practice to randomize dogs based on body weight prior to standard toxicology tests; and (3) Lilly did not know at the outset that it would find a result that may be affected by the estrous stage. Gad Tr. 1764:8-15, 5:15-1766:9; Emmerson Tr. 571:22-572:2, 580:4-581:22. Even Zenith did not randomize by estrous state in conducting its dog study, even though it knew that cholesterol results would be very important. Goldenthal Dep. 162:15-166:13, 168:6-8.

(d) The Length of the Study

234. The length of the D07290 Study was "long enough to recognize a biological [sic] significant effect," Rebar Tr. 2316:21-2317:1, i.e, to study the chronic effects of drug candidates and determine their suitability for repeated-dose studies in humans. Gad Tr. 1757:15-25; Rebar Tr. 2333:22-2334:20. Such preclinical six-month studies had been done at Lilly for both ethyl flumezapine and flumezapine. Emmerson Tr. 543:10-13, 544:23-545:4.

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(e) The Number of Dogs and Analysis by Sex

235. The forty dogs that Lilly used in conducting the D07290 Study were an appropriate number of dogs to use. Rebar Tr. 2316:13-16, 2331:3-12, 2331:24-2332:14.

236. It is standard practice in the scientific community to test toxicity in both male and female dogs and to analyze the results separately by sex. Gad Tr. 1767:3-8; *see also* Pentel Tr. 1914:6-10, 1916:17-1918:11 (agreeing this is common and appropriate); Emmerson Tr. 535:6-11. Indeed, it is required by the FDA. Davidson Tr. 2938:20-2939:14.

237. Lilly used four dogs per sex per group in dog studies submitted to and accepted by the FDA. Emmerson Tr. 535:2-5, 547:15-18, 569:8-10; TX 1005 at ZYP 177 734; TX 1086 at ZYP 661 721; TX 1087 at ZYP 661 1010. Lilly submitted to the FDA a three-month olanzapine study done in 1983, two one-year olanzapine studies (done in 1984 and 1993), and the D07290 Study, that all used four dogs per sex group. Emmerson Tr. 547:15-18, 553:10-11. Lilly also used the same number of dogs in its preclinical testing of flumezapine, which the FDA approved for initial safety and efficacy testing in humans. TX 1005; TX 3421. Four dogs per sex treatment group is a common number of animals to use. Gayheart-Walsten Dep. 35:3-6; Spainhour Dep. 85:8-13; Selim Dep. 19:20-20:22. This sample size was appropriate to perform

statistical analysis and achieve statistically significant results. Thisted Tr. 3061:16-3062:7; Symanowski Tr. 708:2-10.

(f) The Dosage Used

238. At the time of the design for the D07290 Study, there existed considerable experience at Lilly's laboratories with the effects of chronic administration of olanzapine and related compounds in dogs. *See* Engelhardt Dep. 34:3-11 (stating that the dosage for the D07290 Study was selected based on a previous comparison of flumezapine and ethyl flumezapine). As explained above, toxicology testing is traditionally done at or near the MTD, i.e., at higher than therapeutic doses, because the science of toxicology accepts effects in dogs at doses greater than the human therapeutic dose to be reliable indicators of human toxic risk. Gad Tr. 1768:18-1769:5. Comparable toxicology studies done with ethyl flumezapine, flumezapine, and olanzapine prior to actual human testing of those compounds were done at 4, 8, and 12 mg/kg for ethyl flumezapine; at 1, 2, 4, 8, and 12 mg/kg for flumezapine; and at 2, 5, and 10 mg/kg for olanzapine. *See* TX 1002; TX 1003; TX 1004; TX 1005; TX 1040; TX 1041; *see also* LD 22. Thus, the evidence establishes that the 4 and 8 mg/kg doses of compound 222 and olanzapine selected for use in the D07290 Dog Study were well within the objectively reasonable range of preclinical toxicology doses for compounds of this type. Emmerson Tr. 569:4-7; Gad Tr. 1779:24-1780:4; Kanter Tr. 2165:16-2166:18.

239. A one-week pilot study of 8 mg/kg of compound '222 confirmed that the dogs could tolerate 8 mg/kg of compound '222 and that therefore, it was appropriate to proceed with 8 mg/kg of compound '222 as the high dose in the D07290 Dog Study. TX 1164 at ZY 622 344; Emmerson Tr. 569:11-570:1.

(g) The Use of Equal Doses of Olanzapine and Compound '222

240. It was appropriate for Lilly to use equal doses of olanzapine and compound '222 in the Lilly D07290 Dog Study. First, the available *in vitro* and *in vivo* pharmacological data for compound '222 and olanzapine suggested that they would be relatively equally active. *See* TX 1001.1 at FH 125-34, FH 143-45; Tye Dep. 169:17-170:2, 170:24-171:11, 171:13-20 (and errata). Second, one of the objectives of the D07290 Dog Study was to test the hypothesis that these compounds were so similar in structure that they would have essentially the same properties. Nichols Tr. 2860:13-17. The reasonable way to achieve this objective was to test the compounds at equal doses. Killworth Tr. 3022:5-3023:12.

241. Defendants assert the dose for compound '222 was inappropriate as too great a multiple of the human therapeutic dose, and that therefore, the cholesterol results observed in the D07290 Study have no practical relevance. Gad Tr. 1712:2-1713:4; Pentel Tr. 1893:12-17. However, there is no evidence of a

therapeutic dose or safety margin for compound 222 because compound 222 has never been tested in humans. Pentel Tr. 1910:6-10. Moreover, Defendants' experts admitted that dosing the dogs at 4 and 8 mg/kg of compound 222 was reasonable given the fact that olanzapine had been tested at 2, 5, and 10 mg/kg. Gad Tr. 1779:24-1780:4; Kanter Tr. 2165:16-2166:18; LaVoie Tr. 1574:19-1575:16.

(h) How the Study Was Conducted

i) Good Laboratory Practices Were Followed

242. The D07290 Dog Study was carefully conducted in accordance with its protocol and with the FDA's GLP guidelines. 21 C.F.R. § 58; Emmerson Tr. 570:2-4. Lilly maintained complete records. Data reports and logs show careful observation of the dogs and comprehensive consideration of the health of the animals. The D07290 Dog Study was actually reported to the FDA in connection with Lilly's request for approval to market olanzapine. Emmerson Tr. 570:15-24; TX 1164.

ii) Double Rations

243. After observing significant weight loss during D07290 in Dogs 240584 and 242547, two of the female high-dose compound '222 dogs, Lilly researchers gave them double rations of food. Dog

240584 ate her double ration of food 75% of the time. Nachreiner Tr. 1057:2-6, 1057:24-1058:11; TX 3437 at ZY 622 685. Dog 242547 ate her double rations every day of the study but one. Nachreiner Tr. 1057:9-14, 1058:12-22; TX 3437 at ZY 622 687.

244. It is standard toxicology practice to offer increased food rations to dogs to help them maintain their body weight and complete the study. Emmerson Tr. 579:23-580:22; TX 1179 at ZYP 570 152; *see also* Goldenthal Dep. 111:17-112:17 (testifying that MPI generally gives the dogs in studies as much food as they want and then measures the amount they eat); TX 3195.

245. After the double feeding began for these dogs, their cholesterol increased and never came back down to the point it was at before they were double-fed. Emmerson Tr. 613:23-614:4; Symanowski Tr. 734:16-20; Nachreiner Tr. 1060:5-1061:2, 1063:10-21, 1065:4-9.

246. Both dogs regained weight but were continued on double rations throughout the remainder of the D07290 Study. Nachreiner Tr. 1059:16-24.

247. Dr. Bauer testified that feeding dogs increased amounts of Purina 5007 dry dog food, the food offered to the dogs in the D07290 Study in order to maintain their normal body weight, "would have no effect on their blood or total serum cholesterol" because

> that particular type of dry extruded dog food is one that contains only modest amounts of

> its total calories from fat. And feeding — simply feeding larger or increased amounts, even double amounts, of that type of dog food that's very low in its total calories from fat to a dog in order to maintain its normal body weight will not cause an elevation in total blood cholesterol . . . if one wanted to do that by diet, it would take feeding a diet which had a much greater percentage of its total calories from fat in order to elevate the cholesterol in the dog. It's not a question of feeding more of a low or moderate fat diet; it's a question of feeding a diet which contains higher amounts of the total calories from fat.

Bauer Tr. 2682:19-2683:16.

248. The two dogs offered double rations had the lowest cholesterol levels in their group. Symanowski Tr. 706:18-707:8.

249. A similar finding was noted in DRL's Calvert Study. Thisted Tr. 3161:1-9 (testifying that the cholesterol levels in the group of dogs offered double rations of food did not increase); *see also* Findings of Fact § IV.B.7.e(2)(c).

250. Dr. Ronald Thisted ("Dr. Thisted"), Lilly's expert statistician, performed a robustness check removing the two dogs offered double rations, and found that the results remained statistically significant, Thisted Tr. 3085:4-24, as did Dr. Robert Gibbons ("Dr.

Gibbons"), Zenith's expert statistician, using a different method. Gibbons Tr. 2218:24-2220:7; TX 3236 at ZG 13034, 13037; Thisted Tr. 3085:25-3086:8.

251. Although offering double rations to two of the dogs in the D07290 Study caused a difference in the treatment of some of the tested animals which is not ideal, *see* Thisted Tr. 3083:2-3, the evidence establishes that the offer of double rations alone did not confound the results of the D07290 Study.

(i) The Results of Lilly's and Zenith's Studies

i) Statistics Experts for All of the Parties Found a Statistically Significant Cholesterol Increase in the Compound '222-Treated Dogs

252. The statisticians for each of the parties analyzed the data from the D07290 Study and found the cholesterol effect associated with compound '222 was statistically significant over the course of a chronic treatment period. Dr. Symanowski's original repeated measures analysis showed that for cholesterol in the female dogs at the 8 mg/kg/day dose level (a) there was a difference over time between olanzapine and compound '222 that was highly statistically significant, with a p-value of 0.001, (b) there was also

a difference over time between compound 222 and the untreated (control) group that was statistically significant (p 0.001), and (c) there was no statistically significant difference between the olanzapine and control groups. TX 1001.1 at FH 149-54; Thisted Tr. 3079:4-15; Symanowski Tr. 644:12-645:10, 653:17-654:9. The results of Dr. Symanowski's statistical analysis of the D07290 Study have been independently confirmed by both Lilly's statistics expert, Dr. Thisted, and by the Defendants' experts using a variety of methods. Thisted Tr. 3079:16-3082:11, 3085:5-3089:12; LD 391. Dr. McDougall, DRL's expert, replicated Dr. Symanowski's repeated measures analysis and obtained the same results. Thisted Tr. 3080:15-16. Zenith's expert, Dr. Gibbons, used the mixed effect regression method and also found that the high-dose compound '222-treated female group showed a statistically significant increase in mean cholesterol over time compared to both the olanzapine and control groups, but no statistically significant difference between olanzapine and control. Thisted Tr. 3080:17-22; Gibbons Tr. 2214:14-18, 2215:10-2218:22, 2236:4-14; TX 3236 at ZG 12909; LD 391.

253. Dr. Thisted and Dr. Gibbons each analyzed the D07290 data with different modern techniques that allowed them to include both protocol and nonprotocol measurements for all of the dogs. They still found a statistically significant effect of compound '222 in the female high-dose group. Thisted Tr. 3080:23-3082:1; Gibbons Tr. 2216:19-

2217:1, 2218:18-22. They also found statistical significance when they excluded data for the two dogs from the compound '222 group that received extra rations. Thisted Tr. 3085:4-24; Gibbons Tr. 2218:24-2219:24.

254. The results of Zenith's MPI Study confirmed the findings of Lilly's D07290 Study which showed that cholesterol in the female high-dose compound '222 group was significantly greater than in the olanzapine and control groups, whereas the olanzapine group did not differ significantly from the control group. The statistical significance of the results of the MPI Study were found using several different statistical tests. Thisted Tr. 3089:13-3097:19; LD 17; LD 131; LD 381(b); LD 390. Dr. Gibbons confirmed these results as did Dr. Thisted using the GEE analysis. Thisted Tr. 3089:21-3090:12; Gibbons Tr. 2204:3-13. Dr. Thisted also looked at the last four months of the MPI Study, when cholesterol levels stabilized, and found a highly statistically significant difference between compound '222 and both olanzapine and control during that period. Thisted Tr. 3090:13-3092:3; LD 17. MPI's own data tables of the study results show a difference between compound '222 and olanzapine throughout the study (using a statistical test called a t-test), and that compound '222 was statistically significantly greater than control at months two, four, and five (using Dunnett's test). TX 3076; Thisted Tr. 3092:11-3093:4. When the effect of estrus on cholesterol levels in the control group is taken into account, the difference between compound '222 and

control was statistically significant at the three-and six-month time points as well. Thisted Tr. 3095:4-3097:19; LD 381(b). Over the last three months of the MPI Study, the difference between the mean cholesterol values in the compound '222 group and the olanzapine group was about 40 mg/dl, a result also seen in the Lilly D07290 Study. Thisted Tr. 3108:5-3109:6; Gibbons Tr. 2269:8-11.

255. Furthermore, the availability of progesterone measurements in the MPI Study makes it possible to separately evaluate the effects of drug treatment and progesterone on cholesterol. Based on the method of evaluating the progesterone effect set forth by Dr. Raymond Nachreiner ("Dr. Nachreiner"), Zenith's expert in veterinarian endocrinology and reproductive physiology, and based on his own study of the graphs of the individual dogs, Dr. Thisted performed an analysis of the MPI Study data and found that when progesterone effects on cholesterol are filtered out, there is still a highly significant increase in cholesterol in dogs given compound '222. Thisted Tr. 3093:5-3094:12, 3161:16-22. In particular, Dr. Thisted found that the estimated magnitude of the cholesterol elevation, about 40 mg/dl, is about the same whether or not the effect of progesterone is taken into account. Thisted Tr. 3093:5-3094:12. The statistical model that he used, correcting cholesterol for the effects of elevated progesterone one month earlier, was a model proposed by Dr. Nachreiner. Thisted Tr. 3161:16-22.

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256. Dr. Gibbons performed a similar analysis using a different method and also found that after the effect of the estrous cycle on cholesterol was filtered out mathematically, a statistically significant effect of compound 222 remains, with the magnitude of 41 mg/dl. Gibbons Tr. 2220:11-2221:22, 2269:8-11; Thisted Tr. 3094:13-3095:3, 3161:23-3162:4. In addition, he found no statistically significant difference between the olanzapine and control groups. Gibbons Tr. 2221:23-2222:7.

257. Although the shorter DRL Study did not achieve a statistically significant difference between the compound '222-treated dogs and the other groups at the p 0.05 level, the results are not inconsistent with the results of the six-month D07290 and Zenith Studies. Thisted Tr. 3124:20-3126:9; LD 117. All three studies exhibit the same pattern in the first two months, as is shown in LD 117, with a rapid rise in cholesterol in the compound '222-treated dogs and a lesser increase in the olanzapine dogs when compared to the control group. Kanter Tr. 2138:5-16, 2161:20-2163:5. There is no way to tell whether the cholesterol levels in the compound 222-treated dogs in the DRL Study would have stabilized after two months at a significantly higher level than those in the olanzapine and control groups, as was seen in Lilly's D07290 Study and Zenith's Study. Thisted Tr. 3124:20-3126:9.

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ii) The Repeated Measures Analysis Was Appropriate

258. The technique used by Dr. Symanowski to analyze the results of the D07290 Study was the repeated measures analysis of variance. Symanowski Tr. 678:22-679:4, 692:13-19. Dr. Symanowski performed the analysis himself using the statistical analysis system ("SAS") software to directly analyze data in the electronic database. Symanowski Tr. 674:15-675:10.

259. The repeated measures method was more appropriate than the Dunnett's test method for comparing toxicity profiles of olanzapine and compound '222, as was called for originally in the protocol. Symanowski Tr. 682:5-20; 2040:4-9; Thisted Tr. 3059:17-23, 3078:11-19; TX 3439 at ZYP 187 719. The repeated measures method has greater statistical power for detecting differences between treatment groups than does the Dunnett's test. Symanowski Tr. 679:20-680:2. At the time Dr. Symanowski performed his analysis, the repeated measures test was one of the best methods available for analyzing data collected over time. Thisted Tr. 3059:19-21. Even Zenith's statistician, Dr. Gibbons, testified that there was nothing wrong with that method, Gibbons Tr. 2190:1-7, and agreed that it showed a statistically significant increase over time in the cholesterol level of the compound '222-treated group in comparison to both the olanzapine and control groups. Gibbons Tr. 2214:8-13, 2235:18-2236:3.

260. The repeated measures method was well known to the statistical community in 1990, and Dr. Symanowski learned about it during his graduate training. Symanowski Tr. 680:3-14. Dr. Symanowski had previously used the repeated measures method at Lilly before he selected it for use in the D07290 Study. Symanowski Tr. 680:20-681:7. It was an appropriate method for analyzing the D07290 data and was a state-of-the-art method at the time. Thisted Tr. 3059:17-23.

iii) Dunnett's Test Does Not Show that the Effect of Compound 222 Is Small

261. Dr. Gibbons performed Dunnett's test on the data from the D07290 Study and emphasized that at the six-month point he found no statistically significant differences between the high-dose compound '222 females and the controls. Gibbons Tr. 2192:22-2193:14. He considers those results to be consistent with the Zenith Study, of which he says that "there were at the end of the study very small differences between the control and treated animals." Gibbons Tr. 2192:22-2193:14.

262. Dr. Gibbons used an "end point analysis," looking at only the result at the end of the study, whereas Lilly looked individually at every time point, not just the end point, when conducting a Dunnett's test. Gibbons Tr. 2227:4-2228:6.

263. The court does not give weight to Dr. Gibbons' opinion. Dr. Gibbons' end point analysis ignores all, or virtually all, of the data gathered at earlier time points. Gibbons Tr. 2229:1-5. Thus, his analysis ignored the study's purpose, as stated in the protocol, which was to determine over the course of a chronic treatment period whether there was a difference in the toxicity profile between olanzapine and compound '222 in beagle dogs. TX 3439 at ZYP 187 713. In addition, the Dunnett's test has less statistical power or sensitivity than the repeated measures method, because it looks only at data at a single point in time and ignores information from other points in time. Thisted Tr. 3087:19-3088:17; Gibbons Tr. 2229:19-2230:13. A statistically insensitive test can fail to detect statistical significance where a more powerful test will do so. Gibbons Tr. 2230:21-2231:4. Dr. Symanowski's repeated measures method, Dr. Thisted's GEE method, and Dr. Gibbons' mixed effect regression method, all of which showed statistical significance over time, have greater statistical power than Dunnett's test. Thisted Tr. 3088:18-3089:5.

264. Yet, even using the less powerful Dunnett's test, Dr. Gibbons found statistically significant differences between the compound 222 and control groups at months two, four, and five. Thisted Tr. 3086:16-3087:7; Gibbons Tr. 2236:25-2238:18; TX 3236 at ZG012979-84.

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iv) Dr. Gibbons' UPL Test Does Not Show that the Effect of Compound 222 Is Small

265. Dr. Gibbons performed two analyses of the Zenith Study data using the upper prediction limit ("UPL") method and determined that the statistical magnitude of the effect of compound '222 on the cholesterol levels of the high-dose female dogs was small. Gibbons Tr. 2205:17-2212:5. In the first, he determined the UPL for the pretreatment cholesterol values in the Zenith Study and then compared the measurements at the end of the study to those prediction limits. Gibbons Tr. 2208:11-2209:11. In the second, he computed the UPL at the end of the study and compared them to various reference ranges. Gibbons Tr. 2209:12-2210:6.

266. The court finds Dr. Gibbons' UPL method is not an appropriate way to measure the cholesterol results in this case. First, the test only looks at extreme values and ignores all other quantitative information. Thisted 3111:23-3114:21. The bar it sets is high — the upper prediction limit in Dr. Gibbons' analysis of the Zenith data is more than two standard deviations above the mean. Gibbons Tr. 2249:20-2250:16. The UPL test is a statistically weak way of assessing whether there are differences between groups, because it throws away all information about the cholesterol values other than whether they are above or below the line. Thisted Tr. 3119:4-16. Second, there is no evidence

that Dr. Gibbons' UPL analysis has ever been applied to toxicology testing. Thisted Tr. 3121:21-23. Third, UPL analysis has less statistical power than a repeated measures analysis and other techniques (which show a statistically significant difference), and has even less statistical power than Dunnett's test. Thisted Tr. 3119:4-19. Finally, Dr. Gibbons' UPL test ignores the effects of estrus, which is the apparent source of some of the high control and olanzapine values. Gibbons Tr. 2241:3-2242:18; Thisted Tr. 3119:20-24; TX 3236 at ZG 012998.

(j) The Cholesterol Results

267. Dr. John McGrath ("Dr. McGrath"), the senior clinical pathologist on the D07290 Study, Emmerson Tr. 612:11-12, 621:9-11, worked at Lilly as a clinical pathologist from 1979 until his retirement in 2002. McGrath Dep. 6:11-23. He was involved in approximately 50-70 clinical pathology evaluations per year. McGrath Dep. 8:6-23.

268. Dr. McGrath concluded that the most important and biologically significant finding from the D07290 Study was the difference between cholesterol levels measured at 8 mg/kg in the female dogs dosed with compound '222 compared to those dosed with olanzapine. McGrath Dep. 85:13-89:12.

269. Dr. Emmerson, a toxicologist at Lilly for close to thirty years, reviewed Dr. McGrath's conclusion in the context of his overall analysis and consideration

of the results from the D07290 Study. Dr. Emmerson confirmed that there was a real difference in the two compounds based on the pattern of onset, persistence, and magnitude of the elevation of the effect of compound 222 on cholesterol in the 8 mg/kg female dogs. Emmerson Tr. 518:15-21, 583:18-22; TX 1001.1 at FH 142.

i) The Increase in Cholesterol Is Biologically Significant

270. Dr. McGrath's role as a clinical pathologist is to determine, among observed clinical chemistry changes, which of those are of potential biological significance. Rebar Tr. 2308:4-19, 2315:8-2316:15, 2318:15-18 (discussing biological significance); McGrath Dep. 148:14-18 (same).

271. The D07290 Study demonstrated that, of the clinical chemistry changes observed, the increase in cholesterol in the high-dose compound '222-treated female group was of the greatest potential biological significance because of its early onset, persistence, and magnitude. McGrath Dep. 89:3-12, 124:20-125:9. The high-dose compound '222-treated female group exhibited a statistically significant cholesterol increase over time compared to the corresponding high-dose olanzapine-treated group and the untreated control group. The comparable olanzapine-treated group did not show a statistically significant increase compared to the control group over the six-month

study time period. Emmerson Tr. 583:18-22. The magnitude of the mean cholesterol corresponded at study termination to a 40-50 mg/dl increase. TX 1001.1 at FH 152; Thisted 3108:9-3109:6; *see also* Findings of Fact # # 209, 254. The effect was evident early in the study and persisted through study termination. McGrath Dep. 89:3-12; 124:20-125:9.

272. The relationship between total cholesterol and heart disease is fairly linear; the greater the cholesterol level, the greater the risk for heart disease. Davidson Tr. 2933:20-22. A drug that raises cholesterol values in humans "should be avoided unless there's some life threatening condition that would result in a better risk/benefit ratio." Davidson Tr. 2933:5-7. This is especially important to those living with schizophrenia, who face chronic administration of a drug in which many years of therapy could lead to an increased risk for heart disease. Davidson Tr. 2933:8-15.

273. Many antipsychotic drugs, clozapine and olanzapine included, have been noted to be associated with weight gain. It has long been known that some people who gain weight experience an associated rise in cholesterol, and a similar phenomenon has been observed with users of antipsychotic drugs, including clozapine and olanzapine. The discussion of these findings in the recent literature confirms the importance of avoiding antipsychotic drug candidates like compound '222 that have the potential to raise cholesterol directly. Paul Tr. 141:3-142:3, 159:18-

160:17; Davidson Tr. 2905:16-2906:6; TX-3883 ("Given the serious implications . . . attributable to . . . elevated cholesterol, clinicians need to be aware of these risk factors when treating patients with chronic schizophrenia.").

274. Given these facts, the results of the D07290 Study were not only statistically significant, but also biologically significant.

ii) The Increase in Cholesterol Was Not Caused by Other Factors

a) The Female Estrous Cycle

275. Zenith's Dr. Nachreiner testified that due to hormonal changes that occur in female dogs during estrus, the cholesterol levels in these dogs naturally rise. Nachreiner Tr. 1032:19-1033:13; *see also* Gad Tr. 1698:13-16.

276. As mentioned, Lilly did not randomize the dogs involved in the D07290 Study for estrus and did not take the estrous cycle into account when analyzing the data from the D07290 Study. Nachreiner Tr. 1046:2-5; Finding of Fact # 233.

277. The statistical evidence gleaned from Zenith's MPI Study confirmed that the cholesterol effect seen with compound '222 was not attributable to estrus. *See* Findings of Fact # # 209, 254-56.

278. The evidence does not establish that the cholesterol effect seen with compound '222 is attributable to estrus or that the failure to take estrus into account confounded the study results.

b) Double Rations

279. Dr. Nachreiner also testified that the double rations fed to Dog 240584 and Dog 242547 — two of the high-dose compound '222-treated dogs — confounded the D07290 Study results. Nachreiner Tr. 1061:17-1062:8.

280. The evidence reflects that the extra rations fed to those dogs did not affect the cholesterol results from the D07290 Study in a statistically significant manner. *See* Findings of Fact § IV.B.7.e(3)(h)(ii). Therefore, the fact that the dogs were fed double rations did not confound the D07290 Study. This finding is supported by DRL's Calvert Study. Findings of Fact § IV.B.7.e(2)(c).

c) The Alleged Hypothyroid Dog

281. Hypothyroid dogs commonly have elevated cholesterol levels. Nachreiner Tr. 1072:17-22.

282. In a preclinical examination on July 30, 1990, the clinician at Lilly observed that Dog 239924 had a thin, oily coat and the absence of a patellar reflex, all potential symptoms of hypothyroidism. Nachreiner

Tr. 1067:3-10; TX 3454 at ZYP 539 386. This female dog was in the high-dose compound 222 group.

283. Immediately prior to the beginning of the D07290 Study, Dog 239924 was examined again. The record from that examination indicates that the dog was normal at that time. TX 3454 at ZYP 539 386; Nachreiner Tr. 1143:1-20.

284. Lilly's Dr. Jeffrey Engelhardt ("Dr. Engelhardt") personally conducted the histopathology examinations for all of the dogs in the D07290 Study and personally observed the condition of Dog 239924's thyroid gland. Engelhardt Tr. 2275:5-11, 2277:6-8, 2287:1-3. Dr. Engelhardt noted in the contemporaneous necropsy record and testified at trial that the changes in the dog's thyroid gland were not pathologically significant and did not warrant any diagnosis of hypothyroidism. Nor was the dog's coat oily or thin at the time of necropsy. Engelhardt Tr. 2286:6-18. In addition, the symptoms of hypothyroidism are rarely seen in dogs under one year of age, and Dog 239924 was under one year of age at the time of the observed symptoms. Nachreiner Tr. 1142:20-23, 1148:24-1149:9.

285. Zenith's expert, Dr. Nachreiner, testified that there are many other conditions which may present the same physical symptoms (such as an oily, thin hair coat) as hypothyroidism. Nachreiner Tr. 1143:21-24 (stating that a "laundry list" of other conditions could cause these symptoms), 1144:15-1145:12.

286. Dr. Nachreiner did not perform a necropsy on Dog 239924 and thus never observed the condition of the dog's thyroid gland.

287. He also admitted that eight tests necessary to diagnose hypothyroidism in the absence of a biopsy were never performed. Nachreiner Tr. 1145:13-19.

288. Although the dog had "minimal lymphocytic thyroiditis, "Dr. Nachreiner admitted that that condition does not mean that the dog had a hypothyroid. Nachreiner Tr. 1147:23-25; TX 4411 at 486. Indeed, Dr. Engelhardt's observation of "minimal" lymphocytic inflammation meant only that he saw "barely perceptible changes" leaving more than 90% of the gland "normal and intact." Engelhardt Tr. 2288:8-18.

289. The evidence is not sufficient to conclude that Dog 239924 suffered from hypothyroidism.

iii) The Reference Range

290. The reference ranges set forth in Trial Exhibit 1166 were used by Lilly at the time they conducted the D07290 Study. Nachreiner Tr. 1023:12-14; TX 1166.

291. The mean cholesterol values for the dogs in the D07290 Study, including those in the high-dose compound '222 group, were within Lilly's reference ranges. Nachreiner Tr. 1026:2-8, 1183:5-8.

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292. In an experimental study, comparison should be made with the contemporaneous control group in the study. Reference ranges are generally used only when control groups are not available. Rebar Tr. 2366:18-2367:18. In the D07290 and Zenith Studies, cholesterol values from the concurrent controls were reported and available.

293. Reference ranges for any given clinical chemistry parameter are based upon measurements of the parameter in a relatively large group of individuals that are not overtly ill. Thus, the "reference range" represents a range of individual values that might be seen in a population. Gad Tr. 1812:16-1813:1. It is not a range for mean values, nor is it a range of "healthy" values. Gad Tr. 1816: 7-1817:14; Davidson Tr. 2935:25-2936:5.

294. Because the reference range is simply a range of values in a given population, the fact that the mean cholesterol levels of the dogs in the D07290 Study remained within the reference ranges for dog cholesterol does not refute the D07290 Study results.

295. The significance of the finding in the Lilly D07290 Study was that the mean cholesterol value for the whole group increased with compound '222. If a comparable shift in the mean were seen in the human population, such a shift would have a significant detrimental effect on public health. Davidson Tr. 2941:5-2943:23; Thisted Tr. 3106:20-3107:5; LD 329. This would be true even if that increased mean

value were numerically still within the reference range. Rebar Tr. 2320:10-24; Thisted Tr. 3106:6-3107:10.

iv) Other Statistically Significant Changes

296. In addition to the cholesterol finding, Dr. Symanowski's analysis revealed several other statistically significant differences between groups treated with compound '222 and olanzapine. For example, compound '222 slightly increased alanine aminotransferase, gammaglutamyl transferase, and total protein, whereas olanzapine slightly increased several erythrocytic parameters, bilirubin, and albumin. Rebar Tr. 2335:1-2347:21; LD 121; LD 123; LD 124; LD 125; Pentel Tr. 1890:23-1891:4; TX 1171 at ZYP 427 155-56 (showing statistical significance between olanzapine and compound 222 for numerous parameters including ERYS (erythrocytes), HGB (hemoglobin), PCV (packed cell volume), and T BILL (bilirubin)); Symanowski Tr. 723:13-727:13; TX 3451 at ZYP 427 135-37.

297. The determination of whether or not a statistically significant change is clinically significant depends on context. McGrath Dep. 121:2-122:22; Rebar Tr. 2335:8-24.

298. The albumin levels were in the 3.3-3.5 g/dl range. Rebar Tr. 2346:23-2347:3; McGrath Dep. 172:17-21. A clinical pathologist would only be concerned with

these levels if they reached 5 g/dl. McGrath Dep. 172:22-24. Thus, the statistically significant increases in albumin in the male dogs dosed with 8 mg/kg of olanzapine were not biologically significant. Rebar Tr. 2347:4-21; LD 121.

299. The total bilirubin values were in the 0.1-0.2 mg/dl range, but a clinical pathologist would not be concerned until those values were closer to 1.0-2.0 mg/dl. McGrath Dep. 96:3-22; Rebar Tr. 2346:3-12. Thus, although statistically significant, the increases in bilirubin in the male dogs dosed with 8 mg/kg of olanzapine were not biologically significant. McGrath Dep. 96:13-22; Rebar Tr. 2344:5-12; LD 122.

300. The erythrocytic parameters comprising hemoglobin, erythrocyte count, and packed cell volume were also found to be elevated in a statistically significant manner in dogs, but these elevations were not biologically significant. Rebar Tr. 2335:25-2344:2; LD 123; LD 124; LD 125. These three parameters are a measurement of the red blood cell mass in the blood stream, and they usually increase or decrease together, as was the case in the D07290 Study. Rebar Tr. 2336:3-2337:24. Based upon the trends in the data, the olanzapine and control dogs' erythrocytic parameters increased, while the compound '222 dogs' erythrocytic parameters decreased. Rebar Tr. 2338:3-22. While this difference in values between the olanzapine and compound '222 dogs may be statistically significant, the magnitude of the change

was not biologically significant. Rebar Tr. 2338:23-2339:4, 2343:8-24.

301. Of all the changes observed differentiating the compounds, the difference in cholesterol was the most striking difference between olanzapine and compound '222. McGrath Dep. 143:19-144:3, 149:16-22.

v) Dog Data Excluded from the Study Did Not Effect the Study Findings

302. The removal of data from Dog 240712 and Dog 240692, two female dogs in the high-dose olanzapine group, did not confound the statistical analysis of the D07290 Study. *See* Findings of Fact § IV.E.8.

f. Prolactin as a Previously Unconsidered Unexpected Result

(1) The Results of the MPI Study

303. Lilly claims that Zenith's MPI Study showed that compound '222 elevates prolactin whereas olanzapine does not.

304. Prolactin is a hormone that is released from the pituitary gland late in the gestation period to promote lactation in animals. Nachreiner Tr. 1009:8-21.

305. Zenith's study director recommended measuring prolactin after observing mammary enlargement and

lactation in the compound '222-treated dogs. Nachreiner Tr. 1121:22-1122:19. Zenith's protocol was then modified to measure prolactin at months three, four, five, and six, Nachreiner Tr. 1125:21-25, when contemporaneous samples from the control and other groups would be available for comparison.

306. There were no pretest prolactin levels taken for any of the dogs. Similarly, there were no prolactin levels taken for any of the dogs in week one of the study, at month one of the study, or at month two of the study. Concannon Tr. 2601:4-14.

307. Prolactin measurements were taken from the forty-four dogs in the study at month three. Concannon Tr. 2601:16-20. The mean prolactin level in the dogs given compound '222 was statistically significantly higher than the olanzapine or control groups. Nachreiner Tr. 1119:11-1120:9; LD 37.

308. After Zenith obtained those results, the protocol for the study was amended to cancel the rest of the prolactin measurements. Nachreiner Tr. 1126:19-22. Samples for measuring prolactin were taken at month four but never measured. Nachreiner Tr. 1127:11-1128:13.

309. A prolactin measurement that is taken at a single point merely indicates whether a dog is releasing prolactin at that particular point in time, but it does not indicate anything of biological significance. In order to obtain biological significance, there must be measurements

taken at the commencement of the study to establish a baseline level, as well as measurements regarding prolactin release both prior to and after the particular measurement at issue. Nachreiner Tr. 1009:22-1010:7. This did not occur. Thus, the fact that there was a statistically significant difference between the prolactin levels of the dogs given compound '222 and those given olanzapine during month three of the MPI Study, Nachreiner Tr. 1119:11-1120:9, provides insufficient information upon which to make a comparison between the prolactin levels of compound '222-treated dogs and those of the olanzapine-treated dogs. Nachreiner Tr. 1013:12-19; *see also* Gad Tr. 1727:22-1728:1, 1728:22-1729:14.

310. The other observations made by the researchers working on the MPI Study, including excessive mammary development and lactation, Concannon Tr. 2559:2-11, may support the theory of increased prolactin with treatment, but there are no measurements beyond this single point in time to confirm this theory or to indicate its significance. *See* Nachreiner Tr. 1009:22-1010:7; Gad Tr. 1727:22-1728:1.

311. The results of the MPI Study are not sufficiently complete and, as a result, not sufficiently reliable, to support any conclusions regarding the effect of compound '222 onprolactin.

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(2) The Results of the Calvert Study

312. With regard to DRL's Calvert Study, there is no evidence that any prolactin measurements were recorded.

313. Dr. Patrick Concannon ("Dr. Concannon"), Lilly's expert on mammalian reproduction, endocrinology, and physiology, Concannon Tr. 2553:10-22, saw 239 recorded instances of mammary swelling in the compound '222-treated dogs and 195 recorded instances of mammary swelling in the olanzapine-treated dogs. Concannon Tr. 2635:12-21. In contrast, there were only four recorded instances of mammary swelling in the control dogs. Concannon Tr. 2635:22-2636:1.

314. Dr. Concannon saw sixty-one recorded instances of lactation in the olanzapine-treated dogs. Concannon Tr. 2637:1-11. He also observed that the incidence and duration of lactation was greater in the compound '222-treated dogs as compared to the olanzapine-treated dogs. Concannon Tr. 2637:10-2638:15. In the control group, there were no instances of lactation. Concannon Tr. 2637:12-14.

315. The fact that the researchers recorded some lactation and mammary swelling in the dogs during the Calvert Study does not establish a prolactin-related unexpected difference between olanzapine and compound '222.

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(3) Olanzapine's Effect on Prolactin

316. At the time olanzapine was approved by the FDA, its labels stated, and continue to state today, that olanzapine elevates prolactin levels and that a modest elevation persists during chronic administration of the drug. Kinon Tr. 2505:13-22, 2522:5-12, 2525:25-2526:4; TX 3877.

317. When olanzapine was approved, the FDA asked Lilly to include boilerplate prolactin language that was utilized with all first-line antipsychotic agents at that time. Kinon Tr. 2505:13-22.

318. Dr. Bruce Kinon ("Dr. Kinon") is employed by Lilly as a medical advisor and was certified as an expert on the effects of antipsychotic drugs on prolactin. Kinon Tr. 2493:20-23, 2498:7-9. Dr. Kinon testified that since olanzapine's approval, extensive research has confirmed that olanzapine does not elevate prolactin in most patients. Kinon Tr. 2505:25-2506:8. Dr. Schulz agreed that olanzapine does not increase prolactin in patients in any significant way, Schulz Tr. 2978:8-12. He based his opinion on review of the scientific literature in refereed journals, such as the Journal of Clinical Psychiatry. Schulz Tr. 2980:1-5, 2982: 17-24.

319. The olanzapine label still reflects a concern about increased prolactin. TX 3877.

320. Changing a drug's label is a long, expensive, and uncertain process because it is ultimately up to the FDA to determine whether the label will be changed. Schulz Tr. 2983:21-2984:5.

321. The totality of the evidence does not establish that there are prolactin-related unexpected differences between compound '222 and olanzapine.

g. Unexpected Differences Between Olanzapine and Flumezapine

322. Lilly asserted to the PTO that olanzapine unexpectedly failed to abnormally elevate liver (SGOT and SGPT) and muscle (CPK) enzymes in human patients compared to flumezapine. TX 1001.1 at FH 14-15, 17, 45. This claim went unchallenged by the PTO. Zenith now challenges that finding.

(1) Liver and Muscle Enzyme Test Results from the Flumezapine Clinical Trials

323. Lilly first tested flumezapine (compound LY120363) in healthy human volunteers from January through October 1981. TX 3737.

324. Dr. Pullar, a Lilly pharmacologist in the U.K., was chair of the flumezapine project team. Pullar Tr. 166:5-6, 185:20-24. Dr. Lewis Lemberger ("Dr. Lemberger"), a clinical pharmacologist at the Lilly

Laboratory for Clinical Research ("Lilly Clinic") in Indianapolis, was a member of the flumezapine project team. Lemberger Tr. 2449:8-12.

325. Following the second Phase I clinical trials with flumezapine in healthy human volunteers, Dr. Lemberger concluded that flumezapine — in the doses he administered — did not adversely affect the liver enzymes of those healthy human volunteers in a clinically significant manner. Lemberger Tr. 2454:10-15.

326. In the spring of 1982, Lilly commenced its Phase II clinical trials of flumezapine in actual schizophrenic patients at various test sites in the United States, England, and Scotland. TX 1015, TX 3739 at ZY 1762 1383-84. Dr. David Dunner of Seattle, Washington, enrolled one patient; Dr. Jay Cohn of Newport Beach, California, enrolled six patients; Dr. Lawrence Gosenfeld ("Dr. Gosenfeld") of Los Angeles, California, enrolled six patients; Dr. S. A. Montgomery ("Dr. Montgomery") of London, England, enrolled three patients; and Dr. Iain Glen of Inverness, Scotland, enrolled one patient. TX 3739 at ZYP 1383-84; Diamond Tr. 1330:13-17.

327. The data from those five test sites revealed that the enzyme levels in those patients administered flumezapine increased significantly. *See* TX 3739. In particular, four of the six subjects at Dr. Gosenfeld's site experienced CPK (muscle enzyme) elevations that were significant enough to be a concern. Diamond

Tr. 1353:10-23; TX 3739 at ZY 1762 1386 — 1762 1402. In an assay that specified the upper range of normal to be 280, four flumezapine patients (041, 042, 043, and 044) experienced CPK increases up to 5504, 5000, 6352, and 3090, respectively. TX 3739 at ZYP 1762 1393-96.

328. In Lilly's report, Lilly stated that "the elevations of CPK are not well explained . . . Dr. Gosenfeld has reported that, both before, during and after this study elevated CPKs were seen in patients not in the study . . ." TX 1015 at ZYP 177 1999; TX 3739 at ZY 1762 1385.

329. Lilly reported these results to the FDA in April 1982. The FDA advised Lilly to terminate the Phase II flumezapine clinical trials. Pullar Tr. 188:21-23; TX 3259; TX 3260.

330. In December 1985, a joint U.S./U.K. team was set up to find a replacement for flumezapine. TX 1058 at ZYP 520 531.

(2) Liver and Muscle Enzyme Test Results from the Olanzapine Clinical Trials

331. Dr. Lemberger and Dr. Mark Goldberg ("Dr. Goldberg") conducted three Phase I clinical trials of olanzapine in normal human volunteers at the Lilly Clinic in Indianapolis. Goldberg Tr. 355:18-356:9; Lemberger Tr. 2456:8-10; 2456:18-21. The Phase I

clinical trials included HGAA in September 1986, HGAB in February 1987, and HGAC in May 1987. Goldberg Tr. 307:9-308:3; TX 3741 at ZYP 289 1095-96; TX 3742 at ZYP 289 1449.

332. In the interim report for the Phase I clinical trials of olanzapine, Dr. Lemberger reported that five out of eleven patients had elevations in their SGPT and/or SGOT. The doses administered to these volunteers were five to ten times less than those projected to be administered to actual schizophrenic patients. TX 3745 at ZYP 506 148-49; Lemberger Tr. 2466:24-2469:7.

333. In the final report for the olanzapine Phase I clinical trials, Dr. Lemberger stated, "Two of the three subjects completing this study experienced significant elevations in liver enzymes. Based on these results in normal human volunteers, care should be taken to cautiously administer LY170053 [olanzapine] in patients with schizophrenia, with special attention given to the liver enzyme changes that may occur." TX 3744 at ZYP 289 1617; *see also* Goldberg Tr. 361:2-5.

334. Following the conclusion of the tests in healthy human volunteers, Lilly formulated a clinical plan to test olanzapine in actual schizophrenic patients. TX 3688.

335. The study, designated as E001, began in the U.K. in December 1988, and was completed in July 1990. *See* TX 1058; TX 1064.

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336. Dr. David Wheadon ("Dr. Wheadon"), the clinical research physician on the olanzapine project team, reported in April 1990 that both flumezapine and olanzapine had the "propensity to cause elevations in liver enzymes [SGOT and SGPT]." He reported further:

> In the case of flumezapine, these elevations were seen in schizophrenic patients at doses generally higher than 15 mg q.d. . . . Both normal volunteers and patients exposed to LY170053 have, in some cases, experienced elevations in liver enzyme levels. Of the elevations in normal volunteers, one subject experienced this event at a dose of 2.5 mg, the other cases were at doses of 6 mg or higher. In schizophrenic patients, LY170053 was associated with enzyme elevations at a 30 mg dose in one case and a 10 mg dose in two others.
>
> The propensity to cause elevations in CPK appears to be more of a discriminating parameter when comparing these two compounds than elevations in liver enzymes. Admittedly one can argue that had LY170053 been dosed as high as the doses given flumezapine patients, that similar results may have been seen with LY170053. In addition, the literature on elevations of CPK in psychotic patients has featured an ongoing discussion concerning the etiology of this

phenomenon, with some researchers viewing it as a frequently accompanying symptom of psychosis and others noting this elevation to be a neuroleptic side effect.

TX 1063 at ZYP 449 1142.

(3) Dr. Diamond's Opinion

337. Zenith hired Dr. Ronald Diamond ("Dr. Diamond"), a clinical psychiatrist and psychopharmacologist, as an expert for purposes of this litigation. Diamond Tr. 1314:4-13, 1315:1-2, 1325:21-1326:2. Dr. Diamond reviewed Lilly's study data from the flumezapine and olanzapine clinical trials, admitted into evidence as TX 3739, TX 3741, TX 3744, and TX 3747. Diamond Tr. 1326:3-1327:10. He testified that in his opinion, there is no difference between the profile of flumezapine and olanzapine based on liver enzymes. Diamond Tr. 1327:24-1328:9, 1345:22-1346:1.

338. Dr. Diamond reported that with regard to the flumezapine clinical trial, in which schizophrenic patients were given between 0 and 40 mg/day, *see* TX 3739 at ZY 1762 1393 (Patient 41), one group of patients experienced a spike in the elevation of liver enzymes, and the elevation came back to normal after the drug was withdrawn. Diamond Tr. 1347:7-14. Another group of patients experienced a spike during the administration of the drug, but that elevation appeared to return to near normal before the drug was withdrawn. Diamond Tr. 1348:1-16.

339. Dr. Diamond observed these same liver enzyme patterns in the olanzapine clinical trials. Diamond Tr. 1349:4-8, 1350:10-11; TX 3741; TX 3744; TX 3747.

340. Of the fifteen olanzapine subjects reviewed by Dr. Diamond — some normal volunteers and some schizophrenic patients — five had liver enzyme elevations. Diamond Tr. 1351:15-18; TX 3741; TX 3744; TX 3747. Of the fifteen flumezapine subjects reviewed by Dr. Diamond, six had some degree of abnormal liver enzyme elevation. Diamond Tr. 1351:10-14; TX 3739.

341. Dr. Diamond also testified that in his opinion, "there was no reason to believe that there were clinically significant risks from differences in CPK data that was presented in the data." Diamond Tr. 1328:10-12.

342. In support of his opinion, he testified that the elevated CPK levels were all from Dr. Gosenfeld's test site. Diamond Tr. 1390:12-1391:12.

343. Of the four subjects experiencing CPK elevations at the Gosenfeld test site, one of the subjects had elevated CPK levels before taking flumezapine. Diamond Tr. 1354:7-24. This patient began the study with a CPK level of 681 mU/ml, but after 19 days of flumezapine administration, his CPK increased to 5504 mU/ml. TX 3739 at ZY 1762 1393.

344. Also, in all four subjects who experienced elevated CPK, the CPK levels either came down or even

normalized while the subjects continued to take flumezapine. Diamond Tr. 1354:11-15, 1387:20-1389:2. *See e.g.*, TX 3739 at ZY 1762 1393 (Patient 41).

345. The two other test subjects at the Gosenfeld test site, who were tested after the four referenced above, did not experience significant CPK elevations. Diamond Tr. 1353:20-1355:8, 1406:16-20.

346. Lilly did not provide an expert witness to rebut the testimony of Dr. Diamond.

347. The evidence does not support a finding that olanzapine unexpectedly failed to abnormally elevate liver (SGOT and SGPT) and muscle enzymes (CPK) in human patients.

C. Double Patenting

348. The Patent Examiner also rejected the application of the '382 patent based upon obviousness-type double patenting over the claims of the '574 patent in view of *Chakrabarti 1980a*. Killworth Tr. 13-19; TX 1001.1 at FH 53.

349. Double patenting exists to bar an extension of an existing patent monopoly where there is common ownership of both patents. Killworth Tr. 797:3-9.

350. In light of the findings of fact in Section IV.B., the claims of the '382 patent are patentably distinct from

the much broader claims of the '574 patent, even when read in connection with *Chakrabarti 1980a*.

D. Public Use

351. Defendants contend that the Phase I clinical trials of olanzapine in 1986-1987 in healthy volunteers constitute an invalidating public use under 35 U.S.C. § 102(b).

352. As previously stated, Lilly conducted its Phase I clinical trials for olanzapine in healthy human volunteers at the Lilly Clinic. Goldberg Tr. 307:9-308:3; TX 3741 at ZYP 289 1095-96; TX 3742 at ZYP 289 1449.

353. The Lilly Clinic is located in a private ward operated by Lilly at Wishard Hospital in Indianapolis, Indiana. Goldberg Tr. 312:5-7. The Lilly Clinic "looks like a normal hospital," but it is staffed by Lilly employees, and is secured by a security guard. Goldberg Tr. 312:8-24.

354. During the Phase I clinical trials, the volunteers were inpatients at the Lilly Clinic under Lilly's control and observation, but they were allowed to associate with one another, have visitors during restricted visitor's hours, discuss the study with their friends and family, and quit the study at any time. Goldberg Tr. 311:25-312:10, 392:3-10, 392:22-393:2; Lemberger Tr. 2461:1-3.

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355. The volunteers were told only that they were being administered an experimental compound, referred to as LY170053, which was being tested as a possible treatment for schizophrenia. Goldberg Tr. 314:14-23; TX 3741 at ZYP 289 1123-26.

356. The volunteers had no information regarding the chemical composition of olanzapine. They were told neither the structure nor chemical name of olanzapine. Goldberg Tr. 313:2-25.

357. The volunteers were offered, and allowed to take, a copy of the informed consent form. Goldberg Tr. 392:11-16. The informed consent form identified LY170053 as a potential antipsychotic drug. *E.g.*, TX 3741 ZYP 289 1123.

358. While the volunteers understood that their medical records would be treated as confidential, the informed consent form did not state that the volunteers were required to treat the study as confidential. TX 3741 at ZYP 289 1123-26; TX 3742 at ZYP 289 1501-05; TX 3744 at ZYP 289 1667-71; Goldberg Tr. 393:14-20; Lemberger Tr. 2462:9-12.

359. The unrebutted evidence is that the Phase I clinical trials were to determine whether humans could safely take olanzapine. Goldberg Tr. 308:7-12. The protocol for HGAA stated:

> The primary purpose of the present clinical investigation is to cautiously administer

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> Compound LY170053 to normal volunteers in increasing dosage to evaluate its safety and to establish a safe dose for further clinical studies in evaluating the efficacy of LY170053 in psychotic states such as schizophrenia.

TX 3741 at ZYP 289 1113; Goldberg Tr. 318:10-17.

360. Generally, in clinical trials in which it is appropriate, Lilly uses biomarkers, such as the appearance of sedation and/or relaxation to gauge the compound's efficacy in normal subjects. Lemberger Tr. 2447:11-13, 2492:11-13. In the Phase I clinical trials here, Lilly also used biomarkers to evaluate "activity" in the volunteers, i.e., that the compound is being absorbed and having activity in the brain. These indications have "nothing to do with efficacy in the patient population." Lemberger Tr. 2491:21-2492:13.

361. Although the reports from the studies indicate that "several criteria of effectiveness and/or activity, including sedation and/or relaxation, anticholinergic activity, and appearance of side effects were determined by the Modified Cornell Medical Index," TX 3741 at ZYP 289 1087; *see also* TX 3744 at ZYP 289 1614, the credible evidence establishes that the Phase I clinical trials could not, and did not, establish the efficacy of olanzapine. Such efficacy may only be determined by administration of the compound to schizophrenic patients. Lemberger Tr. 2491:21-2492:13, Goldberg Tr. 379:19-380:19. As Lilly's

medical doctor monitoring the Phase I trials explained:

> Olanzapine was targeted for the treatment of acutely psychotic patients that were schizophrenic. Those three trials were done in healthy volunteers [], so one would not be able to detect an antipsychotic effect in a healthy volunteer . . . A healthy volunteer is not psychotic . . . therefore, one would not be able to detect an antipsychotic effect.

Goldberg Tr. 308:20-309:3.

362. Specifically, sedation, observed in the Phase I healthy volunteers, signaled no more than that olanzapine had an effect on the central nervous system — an effect shared by many drugs that are not antipsychotics, such as hypnotics, tranquilizers and opiates. Goldberg Tr. 319:14-22; Lemberger Tr. 2488:15-25.

E. Inequitable Conduct

1. Lilly's Statements to the PTO Did Not Contradict Prior Statements It Made to the Swedish Board of Health

363. Defendants contend that statements made by Lilly to the Swedish Board of Health discounting the toxic effects of olanzapine seen in rats "at large multiples of the clinical dose," contradict statements it made to the PTO regarding the clinical significance of the

cholesterol results from the D07290 Dog Study, as those results were similarly seen only at high doses.

364. In 1990, Lilly sought to conduct human clinical studies of olanzapine in Scandinavia. TX 3169 at ZYP 192 612-20.

365. The Swedish Board of Health expressed concerns about the suitability of human clinical trials due to hematotoxicity found in dogs treated with olanzapine at 10 mg/kg/day. Emmerson Tr. 560:12-22.

366. In November 1990, Lilly filed a written response to this concern. The document is entitled "Response to Comments by Swedish Board of Health Regarding Animal Toxicology Studies With LY170053" ("Response"). TX 3169. It was prepared by Dr. Means and Dr. McGrath. Means Tr. 1992:5-17; TX 3169 at ZYP 192 613. The Response is signed by Dr. Emmerson in his capacity as research fellow for purposes of administrative review, Dr. Means in his capacity as study director of the D07290 Study, and Dr. McGrath in his capacity as senior clinical pathologist for the D07290 Study. Emmerson Tr. 620:22-621:11; TX 3169 at ZYP 192 612, 614.

367. In response to the Swedish Board of Health's comment regarding olanzapine's toxic effects on blood cells and bone marrow, Lilly stated that *"these findings are believed not to have clinical relevance to humans since the effects occurred at large multiples of the clinical dose*, were qualitatively and

quantitatively different among these species [rats, mice, and dogs], and therefore, were not considered to result from a common mechanism." TX 3169 at ZYP 192 615 (emphasis added); Means Tr. 1993:18-22; Emmerson Tr. 621:23-623:10.

368. Lilly elaborated on this answer with a series of comments, based on seven years of extensive analysis and testing relating to blood problems in dogs, mice, rats, and humans, as well as dose level. Different toxicities between different doses was only one of the factors included in Lilly's Response. Emmerson Tr. 620:19-623:10; TX 3169. In particular, Lilly explained that the blood toxicities were only seen in individual dogs, not as a group; the effect appeared to be an immune response; there was no damage to the bone marrow; the effect was reversible upon withdrawal of the drug; the effects were easily detected by blood monitoring; effects in different animals were not due to a common mechanism; cautious tests on humans could proceed with careful monitoring to test if the effect occurred in humans; and the effect did not occur in humans at doses determined to be therapeutic. Gad Tr. 1844:4-1845:21; Emmerson Tr. 564:12-566:14; TX 3169.

369. In reaching its conclusions, Lilly examined blood effects in numerous studies: a three-month study in male and female rats at 22.5 mg/kg/day; a one-year study in male and female rats at 16/mg/kg/day; a three-month study in male and female mice at 45 mg/kg/day; a three-month dog study at 2, 5, and 10 mg/

kg/day; a one-year dog study at 2, 5, and 10 mg/kg/day; bone marrow and antibody studies in affected animals; tests in human volunteers; and tests in actual schizophrenic patients. TX 1085; TX 1086; TX 1087; TX 1091; TX 1092; TX 1093; TX 1122; TX 3169; TX 3574.

370. Lilly's Response satisfied the Swedish Board of Health. Emmerson 624:21-625:4.

371. Lilly did not provide the PTO with its Response to the Swedish Board of Health inquiry. Means Tr. 1994:5-7.

372. Dr. Means and Dr. Emmerson did not inform the PTO in their declarations that any of the results of the D07290 Study should be discounted due to the dosage levels administered to the dogs, as was represented to the Swedish Board of Health with regard to Lilly's previous studies of olanzapine in dogs, rats, and mice. Means 1993:23-1994:1; Emmerson 626:25-627:3; TX 1001.1 at FH 135-42.

373. Lilly's failure to apprise the PTO of this information in its application for the olanzapine patent is not a material omission, and did not contradict its prior statements to the Swedish Board of Health regarding the importance of the dosage of olanzapine and compound '222 administered to the dogs in the D07290 Dog Study, and the cholesterol findings derived therefrom. Lilly's Response to the Swedish Board of Health addressed many factors besides the

dosage levels administered to the animals in the toxicology studies that accounted for the blood toxicity readings. TX 3169. Thus, although the dosage level was one of the factors which led to the blood toxicity readings in the test animals, it was not the only one.

374. Lilly's actions in past studies demonstrate that Lilly regarded toxicities seen at high doses as warranting further study. In fact, Lilly considered terminating the development of olanzapine based on blood problems (neutropenia/ thrombocytopenia) in a single dog administered olanzapine at 10 mg/kg, and spent five years studying that dog. Emmerson Tr. 547:2-549:9, 553:3-4; Pullar Tr. 206:1-19; TX 1086; TX 1092, TX 3475. In another dog study, one dog administered 10 mg/kg of olanzapine developed a blood problem (anemia), and Lilly was again concerned and similarly tested this dog for four years. Emmerson Tr. 553:1-554:11; Pullar Tr. 208:1-210:9; TX 1044; TX 3574. Lilly also twice suspended plans to file an investigational drug application to request permission for human trials based upon the blood toxicity seen in these two dogs at 10 mg/kg. Pullar Tr. 206:1-19, 208:1-210:10.

375. Accordingly, the Response does not support the finding that Lilly believed the cholesterol results of the D07290 Study, particularly those exhibited in the high-dose compound '222 dogs, should be discounted because those results were seen only at the high dose. Indeed, toxicology studies are routinely done at doses

higher than the expected therapeutic dose in humans. Gad Tr. 1768:18-1769:5.

376. There is no clear and convincing evidence that in not disclosing its Response to the PTO during the prosecution of the '382 patent, anyone at Lilly intended to deceive the PTO as to Lilly's beliefs regarding the value of the D07290 Study results.

2. Lilly Did Not Believe that It Was Necessary to Compare Olanzapine and Compound '222 in a Second Species

377. Zenith argues that in Lilly's submission to the Swedish Board of Health, it discounted the toxic effects seen with olanzapine in the dog, because those effects were not seen in the rat. *See* TX 3169 at ZYP 192 615-16. Yet, when it submitted the data from the D07290 Study to the PTO as being predictive of the effects in humans, Lilly did not substantiate this claim by testing compound '222 in another species.

378. The use of multiple species is a regulatory requirement arising from experience and the belief that such use will provide a better chance of detecting the full range of biological responses, adverse and otherwise. Gad Tr. 1846:21-1847:2. This does not mean that an adverse finding must be confirmed in another species before it is considered legitimate and a cause for concern. Indeed, an adverse finding in a particular species requires one to presume that it will

cause an adverse finding in humans unless proven otherwise. Davidson Tr. 2950:13-16, 2951:2-9.

379. There is no clear and convincing evidence that anyone at Lilly believed the results of the D07290 Study were not valid due to the fact that compound '222 was not tested in another species.

380. There is no evidence that the results of the D07290 Study were misrepresented to the PTO with an intent to deceive.

3. Dr. McGrath Believed the Effect of Compound '222 on Cholesterol Was Significant Before Dr. Symanowski Performed a Statistical Analysis

381. Zenith claims that Dr. McGrath did not believe that the effects seen at the high dose in the D07290 Study were important because those effects were seen at significant multiples of the currently proposed human dose, and that his views on this subject were intentionally withheld from the PTO.

382. Lilly's claims of unexpected results in the original patent application were based on Dr. McGrath's observations and conclusions regarding the significance of the cholesterol results. TX 1067 at ZYP 520 935; McGrath Dep. 143:19-144:3, 149:16-150:2. Dr. Symanowski, Lilly's statistician, did not become involved in the study until mid-1991, several months after the U.S. patent application was filed.

Symanowski Tr. 682:5-20, 2040:4-9; Findings of Fact # # 53, 493. Therefore, Dr. McGrath's belief as to the merits of the cholesterol findings are significant. The bases for his findings are below.

383. In his work as the senior clinical pathologist in the D07290 Study, Dr. McGrath evaluated the study data for clinical significance by looking for trends and differences. McGrath Dep. 13:20-21.

384. The official minutes of a prenecropsy meeting for the D07290 Study held on March 29, 1991, which also include Dr. McGrath's handwritten notes, reflect that Dr. McGrath evaluated the study data and found a significant elevation in cholesterol in the female dogs given 8 mg/kg of compound '222. TX 3587; McGrath Dep. 85:13-89:12.

385. Dr. McGrath's notes state on page one that "females increased cholesterol." TX 3587 at ZY 83 627. Further, he testified that, "I had looked at the findings over the course of this study and I believe on the next page [TX 3587 at ZY 83 628] I basically indicated that I felt the cholesterol was increased from Day 62 right through to the end of the study." McGrath Dep. 88:17-20. He further testified that he believed the difference in cholesterol was biologically important at the time of the necropsy meeting: "At that time I felt that it was biologically important. There was a clear distinguishing difference between Triple 2 [compound '222] and olanzapine." McGrath Dep. 88:25-89:2. He explained why he believed the

difference in cholesterol was blatant, "well, for one thing, the magnitude of the values. The other thing was [] the nature of the time course. You know, it occurred early on and then it persisted and it trended upward over time giving greater separation from the controls and from the other compound . . . It was a pretty almost blatant type change when you looked at it." McGrath Dep. 89:3-12.

386. Defendants assert that Dr. McGrath did not believe the effects seen at the 8 mg/kg dose were important. They base their claim on a draft memorandum regarding the D07290 Study dated April 10, 1992, in which Dr. McGrath states, "Increases in primary erythrocytic parameters and total protein appear to be links suggesting an increase in erythropheresis, is this good or bad? Arguments can be made both ways. I feel it's probably not bad since it occurs at *significant multiples of the current proposed human dose.*" TX 1172 at ZY 81 742 (emphasis added). Dr. McGrath describes this memorandum as "very quick and informal," and said that "this is outloud thinking of a clinical pathologist." McGrath Dep. 126:23-127:2, 127:23-128:1 and errata.

387. Dr. McGrath explained that "if you get an increase in primary erythrocytic parameters, that can be a very positive finding in the sense that you have an agent that's enhancing the red cell production in the bone marrow." McGrath Dep. 126:23-127:2. Alternatively, it could be a sign of dehydration, McGrath Dep. 127:2-5, but "with olanzapine at that particular point

in time I had a better feel at least for the hematotoxicity of olanzapine and for the effects on red cell parameters and white blood cell parameters and related parameters." McGrath Dep. 128:14-18. Dr. McGrath continued, "Based on our understanding of [olanzapine] at the time" and the overall circumstances, his reaction was that the increase was probably not bad, in part because of the margin of safety given the dose. McGrath Dep. 127:2-22.

388. Dr. Rebar confirmed Dr. McGrath's ultimate conclusions regarding the results of the D07290 Study. He agreed that the increase in cholesterol was biologically significant, Rebar Tr. 2315:8-16, and that the increase in erythrocytic parameters, although statistically significant, was not clinically significant. Rebar Tr. 2317:15-20, 2335:25-2340:14.

389. There is no evidence that Dr. McGrath believed that the effect seen in cholesterol in the D07290 Study was not important prior to the time that Lilly filed its patent application or prior to the time that Dr. Symanowski ultimately performed his statistical analysis. Thus, there is no clear and convincing evidence that Dr. McGrath's beliefs were intentionally withheld from the PTO with an intent to deceive.

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4. Dr. McGrath's Draft Definition of "Clinical Pathological Significance" Was Not Lilly's Standard for Clinical Significance

390. Zenith argues that Lilly knew that the findings with respect to cholesterol increases occurring only in high-dose compound '222 female dogs did not meet the D07290 Study's definition of "clinical pathological significance" and withheld that information from the PTO with an intent to deceive.

391. In his April 10, 1992 draft pathology report for D07290, Dr. McGrath wrote that "clinical pathological significance is defined as statistically significant differences involving both corresponding compound dose groups and concurrent controls and/or gross deviations from the reference range in individual animals." TX 1172 at ZY 81 740; *see also* TX 3684 at ZYP 209 2577 (a later report, replacing the April 10, 1992 draft).

392. Dr. McGrath testified that the wording in this "very preliminary draft" did not reflect the actual evaluation of the data. McGrath Dep. 121:16-122:22. Dr. McGrath stated that he "never changed how we evaluated the data. It was wordsmithing and there was grammatical enhancement so that a later description more accurately reflected the actual process that I went through." McGrath Dep. 122:18-22.

393. Dr. McGrath's general practice in these types of studies was to look for the "dose response effect," an

effect that could not be examined if the analysis was performed as it appeared to be written in the draft documents. McGrath Dep. 122:1-122:22.

394. Dr. McGrath testified that the same "grammatical problem" existed with his subsequent report dated February 1, 1994. McGrath Dep. 131:16-132:6; TX 3684 at ZYP 209 2577.

395. On February 14, 1995, Dr. McGrath wrote a memorandum indicating his intention to amend the criteria for clinical pathological significance in the interest of clarity and conformity to "correct the grammatical shortcomings of the previous memos and reports." TX 3625; McGrath Dep. 139:8-14.

396. In the final report to the FDA dated May 1995, Lilly defined "clinical pathological significance" as a "statistically significant change in the means of the high-dose group alone and/or in the means of both dose levels of either compound relative to the concurrent controls, and/or gross (moderate-to-marked) deviations from the reference range in individual animals." TX 1164 at ZY 622 356; McGrath Dep. 139:8-140:16.

397. There is no evidence that anyone at Lilly believed that Dr. McGrath's draft document was material to patentability or that it was withheld with the intent to deceive. Similarly, there is no clear and convincing evidence that anyone at Lilly believed that the results

of the D07290 Study were not valid or that they were misrepresented to the PTO with an intent to deceive.

5. Dr. Emmerson Did Not Mislead the Patent Examiner Regarding the Significance of the Results of the D07290 Study

398. Defendants allege that during the interview with the Examiner on December 10, 1992, Dr. Emmerson told the Examiner that olanzapine "was" selected rather than "would have been" selected for development over compound '222 because it showed a lack of cholesterol elevation in female dogs. This misstatement, as alleged by the Defendants, was intended to mislead the Examiner into believing that the D07290 Study had clinical significance.

399. Ms. Vorndran-Jones and Mr. Jones attended the interview with Dr. Emmerson. TX 1001.1 at FH 109-10; Finding of Fact # 70.

400. At the interview, the patent applicants presented eight declarations, one of which was Dr. Emmerson's, to the Examiner. TX 1001.1 at FH 109-10, 125-54. In his declaration, Dr. Emmerson stated he "would not" recommend the clinical development of a compound (like compound '222) that significantly increased the serum cholesterol levels of dogs if there was a compound with similar activity (like olanzapine) that did not. TX 1001.1 at FH 142. Dr. Emmerson testified that he also relayed this fact to the Examiner during the interview. Emmerson Tr. 599:21-24; 631:9-18.

This opinion was also incorporated into Lilly's Response After Final. TX 1001.1 at FH 119.

401. The Examiner's handwritten notes on the Examiner Interview Summary Record state, "[Dr. Emmerson] explained that the instant compound was selected for development because it showed a lack of cholesterol elevation in the female dogs versus the prior art compound (which showed elevated levels in the females)." TX 1001.1 at FH 110.

402. At his deposition, Dr. Emmerson testified that the Examiner Interview Summary Record was "not exactly what I said but it's not — overall, it's not inconsistent." Emmerson Tr. 603.4-16. Dr. Emmerson testified that the Examiner paraphrased his words rather than recording them verbatim. Emmerson Tr. 603:17-22.

403. Ms. Vorndran-Jones never saw the second page of the Examiner Interview Summary Record containing the Examiner's summary of Dr. Emmerson's comments until after this litigation commenced. Vorndran-Jones Tr. 1661:1-1662:7. The two handwritten pages that comprise the interview summary look very similar at first glance. Vorndran-Jones Tr. 1661:14-23.

404. Moreover, although Mr. Jones received a copy of the handwritten summary at the interview, Jones Tr. 1440:10-1441:3; Sofocleous Tr. 958:14-15, he was unsure whether he actually reviewed the document. Jones Tr. 1434:21-1436:1. He stated that his initials

on the page indicated that the Examiner gave him a copy of the document as a "receipt if you will." Jones Tr. 1435:9-10, 1435:24-1436:5.

405. The interview summary stated that no agreement had been reached on patentability and that the Examiner was withholding final judgment on the allowability of the patent "pending [his] final review and analysis of the complete set of data." TX 1001.1 at FH 109.

406. Mr. Jones testified that because the summary did not reflect any agreement with the PTO, it did not require close scrutiny. Jones Tr. 1442:17-1443:7.

407. The declarations and associated response were filed that very afternoon. TX 1001.1 at FH 110-54.

408. Six days after the December 10, 1992 interview, the Examiner telephoned Ms. Vorndran-Jones and advised her that Lilly's application would be in a condition for allowance (i.e., ready to issue as a patent) if she made some typographical corrections. Vorndran-Jones Tr. 1649:12-25; TX 1001.1 at FH 155. Lilly had no additional correspondence with the PTO regarding the D07290 Dog Study following the interview and the filing of Lilly's Response After Final. Vorndran-Jones Tr. 1649:22-25.

409. The Examiner's notes on the Examiner Interview Summary Record do not establish that Dr. Emmerson misrepresented facts during the interview in light of his testimony, the testimony of Ms. Vorndran-Jones,

and the fact that correct statements appear in Dr. Emmerson's declaration and the Response After Final. *See* TX 1001.1 at FH 110, 119, 142; Vorndran-Jones Tr. 1659:2-1666:24; Emmerson Tr. 603:4-604:1, 631:9-18.

410. Further, even if Dr. Emmerson made the misstatement, it was not material given the fact that the Examiner had the opportunity to review, and did review, the Response After Final and accompanying declarations, Vorndran-Jones Tr. 1649:12-21, 1663:2-11, which do not support the statement the Examiner attributed to Dr. Emmerson. *See TX* 1001.1 at FH 112-54.

411. Finally, there is no clear and convincing evidence that during the interview process, or later when the Examiner Interview Summary Record was in the possession of Lilly representatives, that anyone at Lilly intended to deceive the PTO through misstatements of fact or omissions of material fact.

6. Lilly Did Not Mislead the PTO Regarding the Relation Between the D07290 Study in Dogs and the Potential Effects of Cholesterol in Humans

412. Defendants allege that Lilly's Response After Final and supporting declarations, specifically those submitted by Dr. Scruby, Dr. Means, and Dr. Tye, intentionally misrepresented the results of the D07290 Study to the PTO as showing a beneficial effect to

the patient when in fact the D07290 Study provided no basis for such an assertion.

a. Lilly's Representations in the Response After Final

413. Ms. Vorndran-Jones drafted Lilly's Response After Final under the direction of Mr. Jones. Vorndran-Jones Tr. 1635:2-11. At that time, she was a patent associate with Lilly and had not been admitted to the patent bar. Vorndran-Jones Tr. 1615:14-18.

414. The challenged statements in the Response After Final are taken from TX 1001.1 at FH 118-19:

> *The 2-ethyl compound [i.e., compound '222] significantly increases blood cholesterol levels.* Any compound which artificially alters the balance of the synthesis of cholesterol resulting in elevated blood cholesterol is known to be dangerous and undesirable. It is well established that plasma cholesterol is one major factor in the pathogenesis of coronary atherosclerosis. (Clin. Cardiol. 14, 1-40-47 (1991)). Atherosclerosis is a fatal disease for which there is no known cure. (*Ibid.* 14) . . .
>
> *The significance of olanzapine's unforeseen property of treating schizophrenia without artificially elevating cholesterol levels is described in the Declarations of Dr. Emmerson, Dr. Tye, and Dr. Scruby* . . . Any substance which significantly alters the

> balance of the synthesis of cholesterol is likely to have serious consequences on the functioning of the body. Any artificial rise in cholesterol levels caused by the oral administration of such a substance is to be regarded as highly deleterious. *Significantly, olanzapine does not elevate blood cholesterol levels . . .*
>
> Dr. Scruby cites a study which indicated that a 1% reduction in the cholesterol level results in a 2% reduction in coronary artery disease risk. Administration of the '222 compound elevated the cholesterol levels of female dogs between 35% and 40% more than the controls or olanzapine treated dogs. *An increase of such magnitude would significantly alter coronary artery disease risk.*
>
> . . . Dr. Scruby affirms that there is overwhelming evidence in the literature that serum cholesterol in excess of 240 mg/dl is a significant contributor to the genesis of atherosclerosis. *Significantly, olanzapine treats the schizophrenic patient without exposing the patient to the grave consequences associated with a significant increase in cholesterol.*

TX 1001.1 at FH 118 (emphasis added). The italicized statements, read in conjunction with the citation to a medical journal and to the results of other human

clinical studies involving cholesterol in actual human volunteers, create the impression that the use of olanzapine had the benefit of treating patients without the risk of exposing them to elevations in cholesterol and resulting diseases. TX 1001.1 at FH 118-19.

415. Lilly's statements regarding the potential cholesterol effects in humans both in the application, TX 1001.1 at FH 17:24-18:1, and in the Response After Final, TX 1001.1 at FH 112-24, considered in their entireties, were implicitly but clearly based on the D07290 Dog Study and not on actual human clinical trials. Indeed, the Response After Final informed the PTO that human studies of compound '222 had not been conducted and were believed to be unnecessary and unethical. TX 1001.1 at FH 122; Kanter Tr. 2167:18-22. It is also clear in the declarations that statements made about potential effects on cholesterol in humans were based upon the D07290 Study and not on human studies. For example, Dr. Tye's declaration reads in pertinent part, "the compound is clearly and significantly superior to its ethyl analog in so far [sic] as it has been shown in the toxicity study by Dr. Means to lack any tendency to raise cholesterol levels." TX 1001.1 at FH 126. As mentioned, Dr. Means' declaration discusses the D07290 Dog Study. TX 1001.1 at FH 135-39. Dr. Emmerson confirmed this analysis in his declaration when he stated that he "would not recommend the clinical development of a compound which significantly increases the serum cholesterol levels

of dogs when there is a compound with similar activity which does not affect serum cholesterol levels." TX 1001.1 at FH 142.

416. At the time she drafted the Response After Final, Ms. Vorndran-Jones was not aware of any specific publication stating that there is a nexus between dog studies and human studies with respect to cholesterol. Vorndran-Jones Tr. 1623:18-1624, 1632:9-21, 1633:4-16. However, she was well aware of the widespread use of dog toxicology studies as reasonable predictors of the risks to humans associated with administration of pharmaceutical compounds. Vorndran-Jones Tr. 1623:18-24, 1624:5-13, 1632:2-6. This belief was reiterated numerous times throughout the trial by several of Lilly's witnesses. *See*, *e.g.*, Means Tr. 2013:5-9; Scruby Tr. 1462:9-12, 1463:2-4; Tye Dep. 164:23-166:5.

417. During the interview, the Examiner asked only about cholesterol results from the D07290 Dog Study. TX 1001.1 at FH 110. He did not ask questions about cholesterol results from human studies. Vorndran-Jones Tr. 1666:7-12.

418. There is no evidence that the Examiner was in any way misled by Lilly's statements in the Response After Final.

419. There is no clear and convincing evidence that Lilly believed that the D07290 Study results in dogs did not indicate a potential risk to humans and that Lilly

misrepresented the results of the study to the PTO with the intent to deceive.

b. Dr. Scruby's Declaration

420. Dr. Scruby is a medical doctor who has been a staff physician at Lilly since 1983. He is generally familiar with the diagnosis and treatment of coronary artery disease. He has never been involved in any clinical studies involving any drug. Scruby Tr. 1451:10-1452:2; TX 1001.1 at FH 147.

421. On December 2, 1992, Dr. Scruby signed a declaration under 37 C.F.R. § 1.132, which Lilly filed with the PTO on December 10, 1992. TX 1001.1 at FH 146-48; Scruby Tr. 1452:13-25.

422. In his declaration, Dr. Scruby states that he is familiar with the chronic dog toxicology studies described in the declarations of Dr. Means and Dr. Symanowski, that he reviewed their declarations, and that these declarations "provided the basis for my clinical statements concerning the dog toxicology studies." TX 1001.1 at FH 147. Dr. Scruby also relied upon the figures accompanying Dr. Symanowski's declaration. Scruby Tr. 1454:18-1457:1.

423. In addition, Dr. Scruby refers to studies done in humans which link an increase in serum cholesterol to an increased risk of contracting coronary artery disease. Worthy of note is his reference to the Framingham Study, a well-known study

demonstrating the significantly increased risk of coronary artery disease in humans if total cholesterol is in excess of 240 mg/dl. TX 1001.1 at FH 147; Davidson Tr. 2904:3-13.

424. Dr. Scruby concludes:

> . . . The serum cholesterol levels in the female dogs treated with compound '222 after 60 days averaged nearly 260 mg/dl compared with a value of 195 mg/dl with the Olanzapine treated group and 185 mg/dl in the controls.
>
> In view of the overwhelming evidence in the literature that serum cholesterol in excess of 240 ml/dl is a significant contributor to the genesis of atherosclerosis, I believe that these differences in serum cholesterol concentrations would be clinically significant. I believe that the significant elevation of serum cholesterol observed in female dogs treated with the '222 compound could provide a marked clinical difference in the pathogenesis of coronary artery disease.

TX 1001.1 at FH 148.

425. The implication of Dr. Scruby's testimony above is that the increase in serum cholesterol seen in the high-dose compound '222 female dogs can be extrapolated to humans. TX 1001.1 at FH 147-48. Dr. Scruby's use of the Framingham Study's threshold cholesterol

reading, i.e., 240 mg/dl, for purposes of opining the effect serum cholesterol would have on the high dose compound '222 female dogs, is arguably misleading.

426. However, the language in Dr. Scruby's declaration does not claim that there would be a point-by-point extrapolation, nor is there evidence that that is how the Examiner understood it.

427. Dr. Scruby's declaration did not rely solely on the numerical cholesterol values from the D07290 Dog Study and the Framingham Study. Instead, Dr. Scruby pointed out the then-prevailing view that a 1% increase in total cholesterol could carry as much as a 2% increased risk in coronary artery disease, confirming that any increase in group mean cholesterol values associated with compound '222 would be undesirable. TX 1001.1 at FH 147.

428. Dr. Scruby addressed the serum cholesterol elevations in the compound '222-treated dogs and discussed the risk that elevated cholesterol poses in humans. TX 1001.1 at FH 148. Dr. Scruby reasonably concluded that if a similar elevation were seen in humans, it would be clinically significant. Scruby Tr. 1478:24-1479:7. Such an increase would be detrimental in that human patients with increased cholesterol would be at a significantly increased risk of coronary artery disease. Scruby Tr. 1477:10-23.

429. Thus, while Dr. Scruby's use of the Framingham Study's cholesterol readings as a guide to interpreting

the results of the cholesterol readings in the high-dose compound '222-treated dogs may have been misleading, his declaration as a whole was not.

430. Even were his declaration misleading, there is no clear and convincing evidence that he misrepresented or withheld information from the PTO with an intent to deceive.

c. Dr. Means' Declaration

431. Dr. Means has a Ph.D. in pharmacology and toxicology. Means Tr. 1929:9-15. As the study director for the D07290 Study, he was responsible for the technical conduct, interpretation, analysis, documentation, and reporting of the study. TX 1001.1 at FH 136.

432. As part of his duties as study director, Dr. Means received the analysis of the study data from various contributing scientists and compiled that information into a written form for documents that were submitted to regulatory agencies around the world. Means Tr. 2001:11-20.

433. In his declaration, Dr. Means did not inform the PTO that he was not an expert in the area of cholesterol in beagle dogs or that he was relying on Dr. McGrath's analysis. Means Tr. 1991:17-23.

434. Dr. McGrath was never asked to provide a declaration to the PTO, but he provided information on an

ongoing basis to Dr. Emmerson, Dr. Means, and Dr. Symanowski for patent purposes, McGrath Dep. 100:1-8, 150:18-151:6, including the information for Dr. Means' declaration. Means Tr. 1986:3-11.

435. At the time he made his declaration, Dr. Means did not "know with absolute certainty" whether the cholesterol results seen in the dogs in the D07290 Study were predictive in humans. Means Tr. 1996:2-24. However, he had no reason to believe that the results seen in the D07290 Study would not be seen in humans. Means Tr. 2013:5-11. He understood that the dog is a reasonable predictor of what may be seen in humans and that quite often effects seen in dogs are seen in people. He understood that the beagle dog is the large animal model of choice used by Lilly and the pharmaceutical industry. Means Tr. 1998:9-1999:7.

436. There is no clear and convincing evidence that in his declaration, Dr. Means made affirmative misrepresentations of fact, failed to disclose material information, or submitted false information with the intent to deceive the PTO.

d. Dr. Tye's Declaration

437. Dr. Tye has a Ph.D. in behavioral pharmacology. Tye Dep. 6.

438. In his declaration, Dr. Tye stated that he reviewed the results of the D07290 Study and Dr. Means'

declaration setting forth the results he found after reviewing the Study. TX 1001.1 at FH 126.

439. In paragraph 7 of his declaration, Dr. Tye stated, "The data shows significantly increased levels of cholesterol in the case of the ethyl analogue." TX 1001.1 at FH 126.

440. In forming this opinion, Dr. Tye reviewed Dr. Means' declaration and understood that the results reported by Dr. Means were "supported by a statistical analysis by one of [his] colleagues" and that, "as a pharmacologist," he viewed the results of D07290 as "a significant change." Tye Dep. 162:10-23.

441. In paragraph 9 of his declaration, Dr. Tye stated, "The compound is clearly and significantly superior to its ethyl analogue insofar as it has been shown in the toxicity study by Dr. Means to lack any tendency to raise cholesterol levels." The sole basis for this statement is the cholesterol results shown by the D07290 Study. Tye Dep. 174:7-17.

442. Other than for his declaration in this case, Dr. Tye stated that he did not recall ever having made judgments about the safety of a compound under development based on a toxicological finding seen only at the higher dose but not seen at all at the lower dose. Tye Dep. 187:10-15.

443. However, he testified that as a pharmacologist, seeing effects at the 8 mg/kg dose but not the 4 mg/kg dose

told him that there was a dose-response relationship, that the higher dose produces a "bigger effect," and that "if a similar change was observed from the human situation then that would be a serious risk factor." Tye Dep. 186:11-23.

444. Dr. Tye had no reason to distrust Dr. Means' assessments. Tye Dep. 160:5-6.

445. Dr. Tye's reliance on Dr. Means' declaration was reasonable.

446. There is no clear and convincing evidence that in his declaration Dr. Tye made any misrepresentations of fact, failed to disclose any material information, or submitted any false information with the intent to deceive the PTO.

7. Lilly Did Not Mislead the PTO by Withholding Individual Dog Data

447. Zenith argues that Lilly intentionally misled the PTO by not presenting individual dog data that allegedly contradicts Lilly's statements to the Examiner in its Response After Final.

448. On January 27, 1992, Dr. Symanowski generated plots of the individual cholesterol levels for the dogs in the D07290 Study. Symanowski Tr. 2064:8-24; TX 3644.

449. Dr. Symanowski's purpose in making the plots of the individual data for each dog was to look at that data for outliers and to gain confidence in the result of his statistical analysis. Symanowski Tr. 2065:4-22.

450. Dr. Symanowski did not provide any of the plots of the individual data to the PTO when he submitted his declaration. Symanowski Tr. 2068:6-10.

451. To obtain information characteristic of the general population and to study the effects of drug treatments on the population as a whole, scientists conventionally look at *groups* of subjects and calculate descriptive statistics that characterize each group. McGrath Dep. 104:25-105:24 (relating the importance of looking at individual data for gross deviations from the reference range in individual animals); Thisted Tr. 3068:23-3069:6. The *mean*, or average, of a group is a generally accepted and widely used number for comparing differences between groups for both statistical analysis and graphical depiction. Thisted Tr. 3069:7-3070:4, 3070:8-19; Symanowski Tr. 648:20-649:1, 2080:4-16.

452. Individual data points contribute to, and cannot be inconsistent with, the mean. Thisted Tr. 3060:21-3061:8, 3069:15-20; Gibbons Tr. 2244:14-2245:10. There was nothing misleading about Dr. Symanowski not providing the underlying raw data from the D07290 Study to the PTO — the way he presented the data is standard scientific practice. Thisted Tr. 3076:19-24, 3077:7-10, 3077:23-3078:1;

Symanowski Tr. 2079:19-24; Nachreiner Tr. 1188:21-1189:5. There is no evidence that the individual data was not accurately reflected in the mean data Dr. Symanowski reported to the PTO. Similarly, there is no clear and convincing evidence that anyone at Lilly intended to deceive the PTO by not presenting the individual dog data underlying the conclusions of the study.

453. Study protocols describe the manner in which the study is to be conducted, including the number of animals in the groups, the parameters to be studied, and the timing of the sampling from the animals. Symanowski Tr. 657:17-658:4. For example, before a dog toxicology study begins, certain times are picked when blood will be collected from all of the dogs ("protocol bleeds"). Symanowski Tr. 658:5-8. The data taken from all of the test animals on these protocol bleed days is then used to calculate mean or average values for each measured parameter for each group on each protocol bleed day. This is standard scientific practice to avoid bias in the data. Thisted Tr. 3083:2-16; Symanowski Tr. 658:24-659:3. If measurements for calculation of group average values were taken because specific animals looked particularly good or particularly bad (or sick) on the day chosen for the test, it would interject an element of bias into the data tending to artificially favor one group or another. Thisted Tr. 3083:17-3085:3.

454. Dr. Symanowski analyzed the D07290 cholesterol data using only data from blood samples specified in

the protocol. Nonprotocol data from the D07290 Study was not included in the statistical analysis. Symanowski Tr. 695:3-12, 2078:22-2079:18. It never occurred to Dr. Symanowski to provide data from nonprotocol bleeds to the PTO. Symanowski Tr. 2079:19-21.

455. As stated previously in Finding of Fact # 253, Lilly's expert statistician, Dr. Thisted, analyzed the D07290 data, including the nonprotocol data, and found that even with the nonprotocol data there was still a statistically significant elevation of the average cholesterol values in compound '222-treated dogs compared to the olanzapine-treated dogs. Thisted Tr. 3081:8-3082:1. Dr. Gibbons performed a similar analysis with a different method and found the differences remained statistically significant. Gibbons Tr. 2216:19-2217:1. Thus, although that nonprotocol data was not and should not have been included for scientific reasons, even including that data would not have changed the conclusions that Dr. Symanowski presented to the PTO. Thisted Tr. 3082:2-11.

456. Dr. Symanowski's failure to include the individual dog data does was not materially misleading nor done with an intent to deceive the PTO.

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8. Nonprotocol Bleed Data from Moribund Dog 240712 and from Dog 240692 After the End of the Study Taken in Connection with a Bone Marrow Biopsy Are Not Material

457. Zenith argues that Lilly intentionally withheld from the PTO that two of the four high-dose female olanzapine-treated dogs — Dog 240712 and Dog 240692 — had significantly elevated cholesterol levels under Lilly's definition of significance.

458. Early in Lilly's D07290 Study, Dog 240712 developed diarrhea, stopped eating, and became febrile and moribund. Emmerson Tr. 576:13-577:7. The laboratory veterinarian examined the animal and a diagnostic blood sample was taken on study day 27. Emmerson Tr. 577:1-10. The next day, on the advice of the attending veterinarian, the dog was euthanized. TX 1165 at ZYP 538 188. An autopsy confirmed that she was severely ill with pneumonia. Emmerson Tr. 578:21-24; TX 1164 at ZYP 622 634, 994.

459. Between day 8 and day 15, the cholesterol level in Dog 240712 rose from about 135 mg/dl to 185 mg/dl. Symanowski Tr. 2066:23-2067:11; TX 3622 at ZYP 427 2203. Immediately before her death, on day 27, the dog's cholesterol level rose to 396 mg/dl. Pentel Tr. 1881:16-19; TX 3437 at ZY 622 832.

460. In a moribund dog, many clinical chemistry variables may be abnormal. Gad Tr. 1762:8-1764:4; Emmerson Tr. 580:23-581:16. Immediately before this dog died,

many of her clinical chemistry parameters were grossly abnormal. Rebar Tr. 2362:10-2363:25. Thus, the cholesterol reading immediately before she died is not a reliable indicator of the effect of olanzapine and should not have been considered for any comparative purpose. Emmerson Tr. 580:23. Moreover, the day 27 reading was not on a protocol-planned bleed day; therefore, blood was not drawn from the other test animals. Symanowski Tr. 695:14-696:1, 697:18-698:4; Pentel Tr. 1881:16-1882:1; Rebar Tr. 2361:17-2362:9; McGrath Dep. 79:5-80:25.

461. Several dogs involved in the D07290 Study developed cytopenias (generally defined as a major decrease in the number of certain blood cells in circulation). These dogs had additional blood samples taken before and after bone marrow biopsies for the purpose of looking at blood cells and the like. TX 1164 at ZY 622 347-48 and ZY 622 355-56. One of these dogs, Dog 240692, had a cholesterol reading of 327 mg/dl after a bone marrow biopsy on day 188 — four days after the clinical chemistry phase of the D07290 Study had ended. Gad Tr. 1706:14-19; LD 314.

462. Dog 240712 and Dog 240692 had two of the three highest cholesterol levels recorded during the D07290 Study. Gad Tr. 1706:1-4. As discussed above, these high values were recorded as a result of nonprotocol bleeds taken for diagnostic purposes (Dog 240712 at day 27 and Dog 240692 at day 188). Gad Tr. 1706:20-24.

463. As was the case with the isolated measurement from the dying dog (Dog 240712), this isolated measurement of Dog 240692 is not relevant to a comparison of the group effects of compound '222 and olanzapine in cholesterol. Nachreiner Tr. 1169:3-21. Cholesterol values of Dog 240692 remained stable at slightly more than 200 mg/dl for many months, including a value of 216 mg/dl on day 184, the last day on which clinical chemistry samples were taken from all of the dogs. There was an extra unscheduled sample taken from this dog on the next day (day 185); the cholesterol concentration, consistent with the previous measurements, was 209 mg/dl. Rebar Tr. 2365:15-2366:17; LD 314. Then, three days later (day 188), the cholesterol measured in connection with the bone marrow evaluation was 327 mg/dl. TX 1164 at ZY 622 830; *see also* Rebar Tr. 2365:20-2366:10; LD 314.

464. The fact that the dogs' cholesterol had risen prior to any alleged illness — Dog 240712 had an elevation from 134 to 185 mg/dl from day 8 to day 15, and Dog 240692 had a cholesterol rise from 152 to 231 mg/dl from day 8 to day 62 — does not contradict Ms. Vorndran-Jones' assertion that there was no significant cholesterol elevation in any of the olanzapine dogs.

465. The cholesterol levels of Dog 240712 at days 8 and 15 were similar to the mean value of the other olanzapine high-dose dogs, which was reported to the PTO. TX 3622 at ZYP 427 2203. Furthermore,

although Dr. Symanowski's statistical program did not allow him to use the incomplete data from Dog 240712, he performed a robustness check that confirmed to him that those two data points would not have affected the statistical significance of the results. Symanowski Tr. 697:3-15, 701:9-14, 2074:3-15. Both Dr. Thisted and Dr. Gibbons have used modern statistical techniques to show that inclusion of the data from Dog 240712 before it became ill had no effect on statistical significance. Thisted Tr. 3081:8-3082:11; Gibbons Tr. 2216:19-2217:1.

466. With regard to Dog 240692, all of the protocol-defined measurements from that dog were, in fact, used in the statistical analysis that was reported to the PTO.

467. Both Dr. Thisted and Dr. Gibbons have used modern statistical techniques to show that including the nonprotocol cholesterol measurements of Dog 240712 at day 27 and Dog 240692 at day 188 would have no effect on statistical significance. Thisted Tr. 3081:8-3082:11, 3082:15-3084:1; Gibbons Tr. 2216:19-2217:1.

468. There is no clear and convincing evidence that anyone at Lilly withheld these nonprotocol bleed measurements with an intent to deceive the PTO.

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9. A Statement in the Response After Final That There Was No Cholesterol Elevation in "Any" of the Olanzapine-Treated Dogs Was Not Intentionally Misleading

469. Zenith alleges that Ms. Vorndran-Jones misled the PTO by stating in the Response After Final that "similarly, there was no significant cholesterol elevation in any of the olanzapine treated dogs." TX 1001.1 at FH 121.

470. Although the cited sentence does not mention the words "group" or "mean values," TX 1001.1 at FH 121, the only cholesterol data submitted in the declarations which was the subject of the discussion in the Response After Final was group mean data. TX 1001.1 at FH 149-51; Vorndran-Jones Tr. 1639:14-1640:7, 1644:13-19.

471. Ms. Vorndran-Jones testified that as the drafter of the Response After Final, she was merely paraphrasing the declarations. Vorndran-Jones Tr. 1641:10-12. Her paraphrasing is evident from a comparison of the statement in Dr. Means' declaration that he "did not observe any significant elevation in cholesterol levels of the methyl derivative (olanzapine) treated dogs," TX 1001.1 at FH 136, with the statement in the Response After Final that "there was no significant cholesterol elevation in any of the olanzapine treated dogs." TX 1001.1 at FH 121.

472. In addition, the graph of the mean data accompanying Dr. Symanowski's declaration showed on its face some increase (though not statistically significant) in the mean cholesterol values for the olanzapine and control groups. TX 1001.1 at FH 152.

473. There is no clear and convincing evidence that Ms. Vorndran-Jones intentionally misled the PTO by making the subject statement regarding cholesterol findings in the olanzapine-treated dogs.

10. Individual Data from the Control Dogs Does Not Contradict Lilly's Arguments to the PTO

474. Zenith alleges that Lilly intentionally withheld from the PTO individual dog data showing fluctuations in the cholesterol levels of female control dogs. Zenith alleges that changes in the control values contradict Ms. Vorndran-Jones' statement that "there was no significant increase in the blood cholesterol level of any of the control dogs." TX 1001.1 at FH 121.

475. During the dosing period of the D07290 Study, the cholesterol level for Dog 240630 from the female control group ranged from 170 mg/dl to 285 mg/dl. TX 1164 at ZY 622 796. In each of the control female dogs, cholesterol concentrations varied by at least 52 mg/dl over the course of the D07290 Study. TX 3446 at ZYP 427 2201.

476. As with her statement about the olanzapine-treated dogs, Ms. Vorndran-Jones paraphrased what was in the declarations filed by Lilly scientists for purposes of the Response After Final. Vorndran-Jones Tr. 1641:10-12.

477. By definition, group mean data cannot be inconsistent with the individual data from which it was calculated. Thisted Tr. 3069:15-20. Lilly did not provide individual data for any of the dogs from samples defined by the protocol because all of the information from the individual data relevant to the question of whether there was a statistical difference between the groups was incorporated into the information that was provided (mean, standard error, sample size, p-value). Thisted Tr. 3073:1-7; Symanowski Tr. 2079:25-2081:2. Statistical data is customarily reported by group mean, standard error, and sample size, just as Lilly reported it to the PTO, and individual raw data is rarely reported. Thisted Tr. 3076:19-3077:10, 3077:22-3078:1; Nachreiner Tr. 1188:21-1189:5. Furthermore, all of the individual protocol data is incorporated into the means and other data that was reported. Thisted Tr. 3069:15-20.

478. The evidence reflects that the individual data was not inconsistent with the group data summarized by Ms. Vorndran-Jones in the Response After Final, and there is no clear and convincing evidence that her statements were intended to deceive the PTO. Indeed, Ms. Vorndran-Jones never saw the underlying raw data because she relied upon the Lilly scientists/

declarants to interpret it for her. Vorndran-Jones Tr. 1622:1-9. There is also no clear and convincing evidence that anyone involved in the prosecution of the '382 patent considered any individual dog data to be inconsistent with Lilly's arguments before the PTO.

11. Individual Data from Two Dogs Offered Double Rations Did Not Confound the Study Results

479. Zenith alleges that Lilly withheld the fact that two of the high-dose compound '222 dogs — Dog 240584 and Dog 242547 — had elevated cholesterol levels after they began receiving double rations of food.

480. The declaration of Dr. Means disclosed to the PTO that two of the high-dose compound '222 dogs were receiving double rations. TX 1001.1 at FH 137.

481. There is no evidence that any rise in cholesterol was due to the extra rations. *See* Findings of Fact § IV.B.7.e(3)(h)(ii).

482. Further, there is no evidence that the inclusion of the dogs in the study confounded the study results. *See* Findings of Fact § IV.B.7.e(3)(j)(ii)(b).

483. There is no clear and convincing evidence that anyone at Lilly believed that the extra rations affected the cholesterol results and withheld that belief from the PTO with an intent to deceive.

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12. The Change in the Statistical Analysis Protocol from Dunnett's Test to Repeated Measures Was Proper

484. Zenith alleges that Lilly intentionally withheld from the PTO the fact that Dr. Symanowski used a different statistical method (repeated measures) than the one in the protocol (Dunnett's test). Zenith further alleges that Lilly changed its statistical method because it had already informed the PTO that olanzapine was patentable over compound '222 based on the alleged difference in cholesterol effects observed in the D07290 Study, and the only way to show statistical significance was by utilization of the repeated measures test.

485. When Dr. Symanowski joined Lilly, most toxicology studies at Lilly evaluated a single drug and compared the effects of several doses of that drug to a control group. Symanowski Tr. 654:15-656:1. For example, D02093, TX 3628, a one-year dog toxicology study of olanzapine, was a typical study evaluating a single compound at several doses. Symanowski Tr. 741:17-742:6. Generally, studies were conducted over a specified period of time and a standard set of parameters were measured at time points specified in the protocol. Data from the measurements were collected by toxicology personnel, went through a quality control process, and were entered into a computerized system. Symanowski Tr. 654:15-656:1.

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486. An automated analysis and reporting system was used both to conduct statistical analyses and to report the results of the conventional studies. Symanowski Tr. 654:15-656:1. The automated analysis and reporting system was limited to evaluation of just one compound against control. Symanowski Tr. 658:9-12.

487. In approximately 1990, Dr. Symanowski was consulted by the toxicologists on design issues for Lilly's D07290 Study to compare olanzapine and compound '222. Symanowski Tr. 663:17-23. Even though the study was performed for the purpose of a patent application, the overall study design, the number of dogs per group, and the parameters to be measured were standard for Lilly toxicology studies. Symanowski Tr. 666:5-667:2. Before the testing and data collection began, the protocol required testing cholesterol as one of the standard parameters. Symanowski Tr. 667:3-11, 694:2-13.

488. Dr. Symanowski was consulted specifically about the statistical analysis of hematotoxicity, which could not be appropriately evaluated by the automated analysis reporting system because it was an "atypical" parameter, and therefore needed a customized statistical analysis. Symanowski Tr. 663:17-664:2, 668:11-669:13, 713:24-714:21, 2076:17-2077:5. In addition to measuring hematotoxicity, the Lilly scientists intended to measure the standard battery of parameters including cholesterol, but Dr. Symanowski was not asked about and did not recommend any statistical analysis for those parameters at the time

the D07290 Study was being designed. Symanowski Tr. 668:24-669:19, 2076:14-2077:8.

489. At the time the protocol for the D07290 Dog Study was drafted, Dr. Symanowski was not aware that the protocol stated that Dunnett's test would be used to measure clinical chemistry parameters, including cholesterol. Symanowski Tr. 670:20-671:1, 671:11-672:4, 2038:10-17, 2077:6-8, TX 3439 at ZYP 187 719. Dr. Symanowski believes that Dunnett's test was listed in the protocol because it was used in standard studies and was part of the computerized protocol template that was used to plan new studies. Symanowski Tr. 672:5-674:6.

490. After his initial consultation with the toxicologists regarding the design of the comparative dog toxicology study, Dr. Symanowski was not involved in the D07290 Study during the "live phase" when blood and other samples were being taken from the dogs (September 1990-April 1991). Symanowski Tr. 681:17-682:4, 720:5-16; TX 1164 at ZY 622 340; TX 3439 at ZYP 187 712.

491. In Lilly's original patent application filed in April of 1991, TX 1164 at ZY 622 340, those involved with the prosecution of the application represented that compound '222 caused a significant rise in cholesterol levels in four out of eight dogs whereas olanzapine did not. TX 1001.1 at FH 17-18. Similarly, in the IDS, Mr. Ashbrook, Lilly's patent counsel, represented that the invention was patentable over prior art because

of the "surprising biological differences" between compound '222 and olanzapine — specifically, the fact that compound '222 caused a "significant rise in cholesterol levels in 4 out of the 8 dogs which received the compound, whereas [olanzapine] failed to show any rise in cholesterol levels." TX 1001.1 at FH 44.

492. Mr. Ashbrook's statements were based upon the findings of Dr. McGrath, TX 1067 at ZYP 520 935.

493. Sometime in mid-1991, after Lilly filed the patent application, but before the data from the D07290 Dog Study was actually available for Dr. Symanowski to analyze, Dr. Symanowski concluded that the Dunnett's test was not appropriate and that a repeated measures analysis of variance should be used instead. Symanowski Tr. 682:5-20, 2040:4-9. This decision is confirmed by a handwritten memorandum dated September 9, 1991, summarizing Dr. Symanowski's meeting with Dr. McGrath, the clinical pathologist, concerning the D07290 Study. Symanowski Tr. 682:21-684:22; TX 3613.

494. The repeated measures analysis was an appropriate method for analyzing the D07290 data. Thisted Tr. 3059:17-23; *see also* Findings of Fact § IV.B.7.e.(3)(i)(ii).

495. Dr. Symanowski did not tell the PTO that he changed the statistical analysis from that called for in the D07290 Study protocol for clinical chemistry parameters because the Dunnett's test was not capable

of analyzing data to meet the purpose of the D07290 Study, and he did not consider informing the PTO of an incorrect methodology. Symanowski Tr. 2040:13-19; Thisted Tr. 3109:12-3110:2 (expressing his agreement with Dr. Symanowski's decision not to inform the PTO that he did not perform the inappropriate Dunnett's test analysis).

496. When the D07290 Study was formally written up for submission to the FDA in 1994, the study protocol was amended to reflect the change in statistical methodology and was accepted without objection by the FDA. Symanowski Tr. 2042:4-14, 2081:3-2082:2, 2083:12-18; TX 3448.

497. Dr. Symanowski reported to the PTO that, based on his repeated measures analysis of the data from the D07290 Study, he found that the cholesterol in the female dogs treated with 8 mg/kg of compound '222 showed a statistically significant increase over the course of the study when compared to the other groups of dogs. TX 1001.1 at FH 150-51.

498. Dr. Symanowski's decision to perform the repeated measures analysis on the data rather than the Dunnett's test, and his failure to report that change in the study's protocol to the PTO, did not result in an affirmative misrepresentation of fact, the failure to disclose material information, or the submission of false information to the PTO. In addition, there is no clear and convincing evidence that Dr. Symanowski performed the repeated measures analysis and

reported those findings with an intent to deceive the PTO.

13. Dr. Symanowski Did Not Withhold Results Inconsistent with the Results He Presented to the PTO

499. Zenith alleges that Dr. Symanowski performed a "robustness check" to account for the double feeding of two of the four female dogs in the high-dose compound '222 group (Dog 240584 and Dog 242547), and his statistical analysis revealed no statistically significant difference between the cholesterol effects seen in the high-dose compound '222 female dogs versus the control dogs over time. Zenith alleges Dr. Symanowski intentionally misled the PTO by withholding the results of that statistical analysis.

500. After doing his formal statistical calculations involving the data collected in the study, Dr. Symanowski performed "robustness checks" or "exploratory analysis" to confirm the results in his final analysis. Symanowski Tr. 697:10-13. One of Dr. Symanowski's "robustness checks" involved evaluating the data to determine whether the female dogs in the high-dose compound '222-treated group that received double rations affected his analysis. Symanowski Tr. 701:15-17; 2073:17-24, 2074:16-20; TX 3450.

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501. Dr. Symanowski did not report the results of the robustness checks to the PTO because it was not customary to do so. Symanowski Tr. 707:21-708:1, 2060:9-12.

502. The data generated by Dr. Symanowski when performing the robustness checks contains the p-values for the overall averages of different groups over the length of the study. TX 3450. For example, the comparison "mean 053-mean 222" compares the mean for all dose groups of olanzapine with the mean for all dose groups of compound 222 over the length of the study, beginning to end. TX 3450 at ZYP 427 1191; Symanowski Tr. 2056:12-19. The calculation demonstrates no statistical significance in the difference between these groups. TX 3450 at ZYP 427 1191 (indicating p-value of .0609); Symanowski Tr. 2056:12-19.

503. Because, however, the p-values of the "overall average" statistic obtained with the two entirely different methods were so similar, Dr. Symanowski viewed this finding as consistent with, and confirmatory of, the results in his principal analysis. Symanowski Tr. 2055:18-22, 2059:10-13, 2059:19-23, 2075:12-25.

504. There is no clear and convincing evidence that Dr. Symanowski intended to mislead the PTO by withholding the results of his robustness check.

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14. There Was Nothing Misleading About the Use of the Standard Error in Figure 3 of Dr. Symanowski's Declaration

505. Zenith alleges that Lilly misled the PTO by using the standard error instead of the standard deviation in Figure 3 of Dr. Symanowski's declaration. Zenith alleges that the use of the standard error in this circumstance created the false impression that there was a greater difference between the olanzapine, compound '222, and control groups than actually existed.

506. Figure 3 of Dr. Symanowski's declaration is entitled "Profile of Cholesterol Levels. Study D07290." It depicts the mean cholesterol concentrations of female dogs from the control group, the 8 mg/kg olanzapine group, and the 8 mg/kg compound '222 group, plus or minus one standard error. TX 1001.1 at FH 154.

507. Presenting the mean plus or minus a standard error is standard practice in both statistics and biomedical science and is very commonly seen in the scientific literature. Thisted Tr. 3064:11-20, 3098:15-24; Symanowski Tr. 650:23-25; for specific examples *see also* Gibbons Tr. 2255:18-2256:8; Pentel Tr. 1901:17-1902:16, TX 3244; Nachreiner Tr. 1167:7-1168:18; TX 3240, TX 3241; Scanu Tr. 1303:16-1304:24; TX 3214, TX 3246, TX 3131. Dr. Gibbons agreed that the standard error is an important and appropriate estimate of uncertainty, and is an appropriate way to show the precision of a statistical estimate. Gibbons

Tr. 2197:24-2198:12, 2259:3-2260:4. He also agreed that it is appropriate to show the standard error of the mean to describe the uncertainty of a statistical estimate. Gibbons Tr. 2254:11-25.

508. The standard error can be calculated from the standard deviation and vice versa by a simple and well known mathematical formula — the standard error is the standard deviation divided by the number of subjects measured. Symanowski Tr. 653:9-15, 2068:24-2069:9; Thisted Tr. 3072:12-21; Gibbons Tr. 2195:19-22.

509. While a graph illustrating the standard deviation rather than the standard error would have resulted in the shaded areas on Dr. Symanowski's Figure 3 being twice as large for the control-and compound- '222 treated dogs and larger by a factor of the square root of three for the olanzapine dogs, Symanowski Tr. 2068:24-2069:9, there is no evidence that the PTO was misled by Dr. Symanowski's presentation of the data from the D07290 Study. Dr. Gibbons' opinion that the data should have been presented through use of the standard deviation instead of the standard error is not persuasive in light of the credible testimony of Dr. Thisted that Figure 3 was an appropriate and well-accepted statistical method of presenting the data. Thisted Tr. 3065:19-3067:11, 3097:22-3099:6; *see also* Symanowski Tr. 711:11-14, 712:3-8.

510. Nothing in Figure 3 of Dr. Symanowski's declaration to the PTO provided an affirmative misrepresentation

of fact or resulted in the submission of false information to the PTO. Further, there is no clear and convincing evidence that through Figure 3 Dr. Symanowski intended to mislead the PTO.

15. Other Parameters Did Not Show Olanzapine to Be More Toxic than Compound '222

511. Zenith alleges that Lilly intentionally withheld information from the PTO that showed olanzapine to be more toxic than compound '222.

512. Dr. Symanowski found statistically significant increases in certain parameters with respect to male dogs given 8 mg/kg/day of olanzapine compared to male dogs given 8 mg/kg/day of compound '222 and control males in the D07290 Study. Symanowski Tr. 724:22-25; Gibbons Tr. 2198:20-23; TX 3451 at ZYP 427 135-37. These parameters included the erythrocytic parameters (erythrocyte count, hemoglobin concentration, and packed cell volume), total bilirubin and albumin.

513. Dr. Symanowski did not report these statistically significant changes in his declaration to the PTO. Symanowski Tr. 2061:23-25.

514. Dr. McGrath, as the senior clinical pathologist of the D07290 Study, found that the overall pattern of the changes in the erythrocytic parameters, albumin, and bilirubin, were not biologically significant, even though they were statistically significant. McGrath

Dep. 136:14-137:14, 172:6-24; LD 121; LD 122; LD 123; LD 124; LD 125. This finding was confirmed by Dr. Rebar. Rebar Tr. at 2317:15-20, 2335:2-2347:21.

515. In his declaration to the PTO, Dr. Means described these statistically significant changes as "slightly increased." In particular, he averred:

> Male dogs given 8 mg/kg/day olanzapine had slightly increased values for primary erythrocytic parameters (erythrocyte count, hemoglobin concentration, and packed cell volume), total bilirubin, and albumin.

TX 1001.1 at FH 138.

516. Dr. Means based his statement above on the information he received from Dr. McGrath. Means Tr. 2008:14-19; 2009:5-16.

517. Dr. Means' reliance on the findings of Dr. McGrath was reasonable.

518. There is no clear and convincing evidence that anyone at Lilly believed that the increases in the erythrocytic parameters, albumin, and bilirubin, observed in the high-dose olanzapine-treated male dogs, were biologically significant. Therefore, there is no clear and convincing evidence that Dr. Symanowski's failure to apprise the PTO of the statistically significant increases observed in these parameters was

a material omission of fact made with an intent to deceive. There is also no clear and convincing evidence that Dr. Means' use of the descriptive phrase "slightly increased" was a material misrepresentation made with an intent to deceive the PTO.

16. The Reference Range for Cholesterol Is Not Material and Was Not Intentionally Withheld from the PTO

519. Zenith alleges that Lilly intentionally failed to disclose that the significantly elevated cholesterol levels in the compound 222-treated female dogs were within the cholesterol reference range for female dogs.

520. Dr. McGrath used reference ranges at Lilly to select animals and in making assessments of parameters tested for the evaluative process. McGrath Dep. 14:11-24.

521. As noted in Finding of Fact # 291, the mean cholesterol values that Lilly presented to the PTO in relation to the high-dose compound 222 dogs were within Lilly's own reference range. Nachreiner Tr. 1183:5-8.

522. Lilly did not disclose this information to the PTO. Nachreiner Tr. 1183:9-10.

523. The information regarding the reference range was not material to the decision of patentability by the PTO. No Lilly representative made statements to the

PTO, through declaration or otherwise, about the reference ranges for dog cholesterol. The significant data from the D07290 Study, as Lilly presented in its Response After Final and accompanying declarations, was an increase in group mean values in the compound 222 group in comparison to the olanzapine and control groups. Further, there is no clear and convincing evidence that Lilly's decision not to discuss the reference range with the PTO was in any way intended to deceive the PTO.

17. There Was No Inequitable Conduct Regarding the Failure to Disclose the Phase I Clinical Trials

524. Zenith alleges that Lilly intentionally withheld information about the Phase I clinical trials involving olanzapine because the results of these trials reveal that the '382 patent is invalid.

525. The clinical trials were not a public use of olanzapine and were for experimental purposes only. Therefore, there was no reason to disclose information about them. *See* Findings of Fact § IV.D.

526. There is no clear and convincing evidence that anyone at Lilly considered the clinical trials material prior art or concealed them with the intent to deceive the PTO.

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18. There Was No Inequitable Conduct Regarding Lilly's Failure to Disclose the 574 Patent and the *Chakrabarti* Articles

527. Zenith alleges that Lilly intentionally withheld material prior art, specifically, the 574 patent and *Chakrabarti 1980a*. DRL alleges that Lilly intentionally withheld two material prior art publications, *Chakrabarti 1982*, and *Chakrabarti 1989*.

a. *Chakrabarti 1980a* and the 574 Patent

528. Lilly did not disclose the *Chakrabarti 1980a* article or the '574 patent to the PTO during the prosecution of the '382 patent. TX 1001.1 at FH 44-45.

529. Lilly did disclose the '568 patent to the PTO and specifically explained that "the reference fails to disclose the compound which is now claimed, but does describe the adjacent homologue [compound 222]." TX 1001.1 at FH 44.

530. The technical disclosures of the 574 and 568 patents are identical and each discloses the genus of compounds that generically includes olanzapine. Tupper Tr. 431:4-17; TX 1408, 3129. Moreover, Lilly cited the British counterpart of the '574 and '568 patents in the olanzapine patent application. Killworth Tr. 770:18-771:6. When the British counterpart is put into the computerized database that correlates U.S. patents with their foreign counterparts, the first U.S.

counterpart that the computer identifies is the 568 patent followed by the 574 patent. Killworth Tr. 771:7-772:20. This database is well known and available to patent practitioners. Killworth Tr. 772:21-773:4.

531. In the PTO's first Office Action related to the olanzapine patent application, the Examiner cited and relied upon both *Chakrabarti 1980a* and the '574 patent in arriving at his decision to reject the claims of the application. TX 1001.1 at FH 104-05.

532. There is no clear and convincing evidence that anyone at Lilly withheld the '574 patent and/or *Chakrabarti 1980a* with an intent to deceive the PTO.

b. *Chakrabarti 1982* and *Chakrabarti 1989*

533. Lilly did not disclose *Chakrabarti 1982* or *Chakrabarti 1989* to the PTO during the prosecution of the olanzapine patent. TX 1001.1 at FH 44-47.

534. Those articles were part of a series that began with *Chakrabarti 1980a* and ran through *Chakrabarti 1989*, and in which the authors expressed a clear preference for fluorinated compounds. Nichols Tr. 2749:1-2750:9.

535. The only compounds discussed in *Chakrabarti 1982* were twelve thienobenzodiazepines with a fluorine at the 7-position, TX 3131 at 1137 Table I; Reith Tr. 916:2-16, and the authors expressed a clear preference

or interest in two of those compounds, flumezapine and ethyl flumezapine. Nichols Tr. 2749:1-24; TX 3131 at 1137 (stating that compounds 2 and 9 "demonstrate potent antidopaminergic, as well as anticholinergic, activity").

536. *Chakrabarti 1989* looked at a completely different series of compounds (pyrazolobenzodiazapines, not thienobenzodiazepines) and reported that the (fluorinated) flumezapine compound was selected for clinical trial. Nichols Tr. 2749:25-2750:9; TX 3132 at 2574. *Chakrabarti 1989* did not mention olanzapine, ethyl flumezapine, or compound 222. Dr. Reith testified that one of ordinary skill in the art "would *not* apply the information from this set of compounds [i.e., the pyrazolobenzodiazapines in *Chakrabarti 1989*] to, for example, the family of compounds in the 1988 [sic — 1980a] *Chakrabarti* article." Reith Tr. 922:9-923:3 (emphasis added).

537. *Chakrabarti 1982* states that "[a] small alkyl substitution in the 2-position of the thiophene ring enhances the antidopaminergic activity." TX 3131 at 1134. This statement was a reference back to the data that had been reported in *Chakrabarti 1980a* and which was considered by the Examiner. This is clear from the text of *Chakrabarti 1982*, which reiterates that "recently, we have reported" the data in *Chakrabarti 1980a*, and specifically cites to the 1980 article in a footnote. TX 3131 at 1133 n.6. This statement in *Chakrabarti 1982* was therefore cumulative and by definition not material. Killworth

Tr. 766:2-22 (defining cumulative). No witness testified to the contrary.

538. *Chakrabarti 1989* states that "a short alkyl group at position 2 greatly enhanced activity." TX 3132 at 2576. This statement, like that in *Chakrabarti 1982*, was a reference back to old data that had previously been reported in *Chakrabarti 1980a*. This is clear from the text of *Chakrabarti 1989*, which specifically cites to the 1980 article in a footnote. TX 3132 at 2574 n.2, 2576. This statement in *Chakrabarti 1989* was therefore cumulative and by definition not material. Killworth Tr. 766:2-12.

539. Dr. LaVoie confirmed this analysis when he explained that *Chakrabarti 1980a* stated that a "short alkyl group [at the 2-position] seemed to increase activity," and later testified that the authors of *Chakrabarti 1982* "again" made a "similar disclosure" that was "consistent with the previous comments." LaVoie Tr. 1522:22-1523:2. With respect to *Chakrabarti 1989*, Dr. LaVoie testified that it also included a similar disclosure. LaVoie Tr. 1523:3-6.

540. DRL's references to the statements made in *Chakrabarti 1982* and *1989* regarding the desirability of a short alkyl substitution at position 2 of the thiophene ring do not refute any argument made by Lilly. In its Response After Final, Lilly did not controvert the PTO's assertion that olanzapine would have been suggested by the cited prior art, choosing instead to present evidence of unpredictable and

unexpected side effects associated with compound 222. The various *Chakrabarti* articles say nothing that bore on the issue of the cholesterol-elevating side effect of compound 222. *See* TX 1001.1 at FH 112-24; TX 3131; TX 3132.

541. There is no clear and convincing evidence establishing that *Chakrabarti 1982 or Chakrabarti 1989* were material to patentability or that anyone at Lilly concealed those publications with the intent to deceive the PTO.

CONCLUSIONS OF LAW

1. To the extent any of the foregoing findings of fact is a conclusion of law, it is hereby adopted as a conclusion of law. To the extent any of the conclusions of law set forth below is a finding of fact, it is hereby adopted as a finding of fact.

I. Controlling Authority

A. Jurisdiction

2. The court has subject matter jurisdiction over this case pursuant to 28 U.S.C. §§ 1331 and 1338(a).

3. The 1984 Hatch-Waxman amendments to the Federal Food, Drug, and Cosmetic Act regulate the process by which generic drug companies gain approval from the FDA to bring generic pharmaceuticals to market. 21 U.S.C. § 355.

4. The filing of an application with the FDA under 21 U.S.C. § 355 for a drug claimed in a patent or the use of which is claimed in a patent is an act of patent infringement if the intention of the applicant is the commercial manufacture, use, or sale of the drug before the patent expires. 35 U.S.C. § 271(e)(2)(A).

5. An applicant must make a certification with respect to the patents that cover the drug that the generic product which is the subject of the application will not infringe the patents or that the patents are invalid. 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

6. Upon receiving notice of the applicant's certification regarding the patents, the patent holder may bring an action in the United States District Court for a declaration of whether the applicant will infringe the patent. *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1570-71 (Fed. Cir. 1997).

B. Federal Circuit Law Applies

7. Any appeal in this action, which arises under the patent laws of the United States, must be to the United States Court of Appeals for the Federal Circuit, 28 U.S.C. § 1295(a), whose precedent governs matters of substantive patent law in this court. The Federal Circuit has adopted decisions of the Court of Customs and Patent Appeals ("C.C.P.A.") as its own precedent, making those decisions binding on this court. *E.g.*, *Southwire Co. v. Essex Group, Inc.*, 220 U.S.P.Q. 1053, 1056 n.6 (N.D. Ill. 1983) ("The law that

controls this action . . . ared that the patent decisions of [the C.C.P.A.] will be considered binding. . . .") (citing *South Corp. v. United States*, 690 F.2d 1368, 1370 (Fed. Cir. 1982) (en banc)).

C. The Presumption of Validity

8. Patents are presumed valid. Each claim within a patent is independently presumed valid, even if other claims within the patent are held invalid. 35 U.S.C. § 282.

9. The burden of proving invalidity rests on the patent challenger, who must do so by clear and convincing evidence. 35 U.S.C. § 282; *Schumer v. Lab. Computer Sys., Inc.*, 308 F.3d 1304, 1315 (Fed. Cir. 2002).

10. "The 'clear and convincing' standard of proof of facts is an intermediate standard which lies somewhere between beyond a reasonable doubt' and a preponderance of the evidence'" and "has been described as evidence which produces in the mind of the trier of fact an abiding conviction that the truth of [the] factual contentions are highly probable.'" *Buildex Inc. v. Kason Indus., Inc.*, 849 F.2d 1461, 1463 (Fed. Cir. 1988) (internal quotation omitted).

11. The burden "is constant and remains throughout the suit on the challenger" and "does not shift at any time to the patent owner." *TP Labs., Inc. v. Prof'l Positioners, Inc.*, 724 F.2d 965, 971 (Fed. Cir. 1984).

12. If a patent challenger alleges invalidity based on the prior art the PTO considered during prosecution of the patent, that challenger has the

> added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents.

Ultra-Tex Surfaces, Inc. v. Hill Bros. Chem. Co., 204 F.3d 1360, 1367 (Fed. Cir. 2000) (quoting *Am. Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1359 (Fed. Cir. 1984)). In other words, "the challenger's burden is especially difficult when the prior art was before the PTO examiner during prosecution of the application.'" *Al-Site Corp. v. VSI Int'l, Inc.*, 174 F.3d 1308, 1323 (Fed. Cir. 1999) (quoting *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1467 (Fed. Cir. 1990)).

D. Selection Inventions

13. Selection inventions, also referred to as "improvement patents," are a normal consequence of technological progress and are expressly provided for by statute. 35 U.S.C. § 101 ("Whoever invents . . . any new and useful . . . composition of matter, or any . . .

improvement thereof . . . may obtain a patent therefor . . .") (emphasis added).

14. Inventions based on the identification or selection of a specific material or compound with particularly desirable properties within a previously disclosed genus of such materials or compounds do not violate any of the substantive requirements for patentability. *See e.g.*, *In re Ruschig*, 343 F.2d 965, 974-75, 52 C.C.P.A. 1238, 1965 Dec. Comm'r Pat. 482 (C.C.P.A. 1965) (prior generic disclosure did not anticipate later selected species under 35 U.S.C. § 102); *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1340 (Fed. Cir. 2003) ("Improvement and selection inventions are ubiquitous in patent law . . ."); *In re Kaplan*, 789 F.2d 1574, 1578, 1580 (Fed. Cir. 1986) (prior generic patent claim did not invalidate claim to later selected species for double patenting); *In re Baird*, 16 F.3d 380, '382 (Fed. Cir. 1994) (prior generic disclosure did not render later selected species obvious under 35 U.S.C. § 103).

II. The Validity of the '382 Patent

A. Anticipation — Lack of Novelty under 35 U.S.C. § 102

15. Title 35 U.S.C. § 102(b) states that a patentee shall be entitled to a patent unless "the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for a patent in the United States."

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16. A claim not satisfying the novelty condition of patentability, as defined in § 102, is said to be "anticipated." *E.g.*, *Oakley, Inc. v. Sunglass Hut Int'l*, 316 F.3d 1331, 1339 (Fed. Cir. 2003).

17. A printed publication will anticipate a claim under § 102(b) only if "each and every [claim] limitation is found either expressly or inherently in a single prior art reference." *Celeritas Techs. Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1361 (Fed. Cir. 1998). In other words, a printed publication must include all the "limitations," i.e., defining features of the claim, as those limitations are arranged in the claim. *See, e.g.*, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989). Merely identifying within the prior art all of the various parts of the claimed subject matter is not anticipation. Instead, "there must be *no difference* between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991) (emphasis added).

18. If a claim limitation is not found expressly in a prior art reference, the court may inquire as to whether the missing descriptive matter is necessarily inherent in the thing described in the reference. *Cont'l Can Co. U.S.A., v. Monsanto Co.*, 948 F.2d 1264, 1268-69 (Fed. Cir. 1991). Although extrinsic evidence may be referred to "to explain the disclosure of a reference," the Federal Circuit has stated that "the role of extrinsic evidence is to educate the decision-maker to what the

reference meant to persons of ordinary skill in the field of the invention, not to fill gaps in the reference." *Scripps*, 927 F.2d at 1576; *see also Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 716 (Fed. Cir. 1984) (rejecting argument that "missing elements may be supplied by the knowledge of one skilled in the art or the disclosure of another reference").

19. An anticipatory reference need not be from analogous art as long as it explicitly or inherently discloses every limitation recited in the claims. *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997) (rejecting the patentability of a structure for dispensing popcorn because it was already disclosed in a prior patent "regardless of whether it has ever been used [or disclosed] in any way in connection with popcorn").

20. Inherent anticipation "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981) (quoting *Hansgirg v. Kemmer*, 102 F.2d 212, 214, 26 C.C.P.A. 937, 1939 Dec. Comm'r Pat. 327 (C.C.P.A. 1939)). To be inherent, an undisclosed feature must necessarily and inevitably flow from practice of what is disclosed. *Id.*

21. The question of whether a printed publication includes all of the claim limitations, expressly or inherently, is a question of fact. *Minn. Mining & Mfg. Co. v.*

Chemque, Inc., 303 F.3d 1294, 1301 (Fed. Cir. 2002); *Schreiber*, 128 F.3d at 1477.

1. *Chakrabarti 1980a* Does Not Anticipate the Claims of the '382 Patent

22. Defendants have failed to prove by clear and convincing evidence that *Chakrabarti 1980a* anticipates any claim of the '382 patent.

23. The parties agree that *Chakrabarti 1980a* does not expressly describe olanzapine. Instead, Defendants contend that one of ordinary skill in the art, applying the preferences expressed in *Chakrabarti 1980a*, would envision a very small group of compounds, one of which is olanzapine.

24. Because *Chakrabarti 1980a* was before the PTO during the prosecution and was not deemed anticipatory by the PTO, Defendants have the added burden of "overcoming the deference due to a qualified government agency presumed to have done its job." *See Ultra-Tex Surfaces*, 204 F.3d at 1367. That burden "is especially difficult" to meet. *Al-Site*, 174 F.3d at 1323.

a. *Chakrabarti 1980a* Does Not Disclose a Genus

25. Disclosure of a genus of chemical compounds generally does not anticipate a claim to a particular species within that genus because picking and

choosing from among the possible options is required to arrive at each species in the genus. 1 Donald S. Chisum, *Patents* § 3.029209b0 (2003) ("This suggests that a prior genus which does not explicitly disclose a species does not anticipate a later claim to that species.").

26. A narrow exception to this general rule was first articulated in *In re Petering*, 301 F.2d 676, 49 C.C.P.A. 993, 1962 Dec. Comm'r Pat. 232 (C.C.P.A. 1962), a case upon which Defendants rely.

27. In *Petering*, the court affirmed the rejection of a claim to a specific compound, 6, 7-dimethyl-9-[[beta]-monohydroxyethyl]-isoalloxazine. In addition to finding that the prior art reference, known as the Karrer patent, disclosed a generic disclosure of isoalloxazine derivatives, the court also found the Karrer patent disclosed "certain specific preferences . . . through [a] series of preferred R groups and [its] eight specific isoalloxazines." *Id.* at 681. The court went on to find that

> the pattern of Karrer's specific preferences [for the six variable substituents on the generic formula] in connection with his generic formula constitutes a description of a definite and limited class of compounds which may be defined with reference to the Karrer generic formula as follows: where X, P and R' are hydrogen, where Y and Z may be hydrogen or methyl, and where R is a

member selected from the group consisting of -CH2OH, -CH2CH(OH)CH2OH, -CH2CH2OH, -CH2(CHOH)3CH2OH and -CH2(CHOH)4CH2OH.

Id.

The court further explained that the "pattern of preferences" permitted only a "limited number of variations for R, only two alternatives for Y and Z, no alternatives for the other ring positions, and a large unchanging structural nucleus." *Id.* at 681-682. The court therefore held that "Karrer described to one skilled in the art a limited class of some 20 compounds, including 6, 7-dimethyl-9-[[beta]-monohydroxyethyl]-isoall oxazine, as fully as if he had drawn each structural formula or had written each name.'" *In re Schaumann*, 572 F.2d 312, 315 (C.C.P.A. 1978) (quoting *Petering*, 301 F.2d at 681).

28. Defendants also rely on *Schaumann*, supra. In that case, the court found the invention anticipated where claim 1 of the reference patent contained a formula describing a narrow subset of the disclosed compounds with only one variable denominated "R" and further specifying that "R" was a "lower alkyl" group. The patent text defined the R as including seven specific lower alkyl groups, rendering all seven anticipated. The *Schaumann* court, relying almost exclusively on *Petering*, held that the printed publication "embraces a very limited number of compounds closely related to one another in

structure," therefore "we are led inevitably to the conclusion that the reference provides a description of those compounds just as surely as if they were identified in the reference by name." *Id.* at 316-17.

29. Thus, in both *Schaumann* and *Petering*, the prior art reference was an issued patent that contained a true generic disclosure, like the fully defined formula in the 574 patent, that (1) squarely encompassed the later claimed compound, and (2) represented (without contradiction from the prior art) that it would work.

30. In contrast, *Chakrabarti 1980a* is an article that does not define any genus at all, much less a small preferred genus of compounds that would include olanzapine. *Chakrabarti 1980a* does provide a general chemical formula with substitutions at three locations (denominated as "R", "R1", and "R2"), but these substituents are not generically defined as they were in *Schaumann* and *Petering*. Further, only particular substituents at each of these places are disclosed and the forty-five compounds created as a result of those substitutions are presented in a table in the article. These compounds do not represent a genus, simply forty-five compounds the authors chose to create and test. None of the forty-five listed compounds is olanzapine. *Cf. Petering*, 301 F.2d at 681-82; Findings of Fact § IV.A.1.

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b. The Preferences Expressed in *Chakrabarti 1980a* Do Not Lead a Person of Ordinary Skill in the Art to Envision Olanzapine

31. In addition, Defendants have failed to prove by clear and convincing evidence that any preferences actually expressed in *Chakrabarti 1980a* would have led a person of ordinary skill in the art to necessarily envision olanzapine.

32. *Chakrabarti 1980a*, as stated previously, does provide a general structural formula with possible substituents of "R", "R1", and "R2" without defining them. The reference further expressly states that specific substituents were preferred: R is preferably a methyl, hydroxyethyl, or hydroxypropyl; R1 is preferably a fluorine, chlorine, or 7, 8, di-fluoro; and R2 is preferably a methyl, 2-ethyl, or 2-isopropyl group. No possible combination of those preferred substituents would lead to the components that make up olanzapine, because each would contain a fluorine or a chlorine. *Cf. Schaumann*, 572 F.2d at 316-17.

33. Nor have Defendants offered any evidence that a person of ordinary skill in the art would envision olanzapine from five individually "preferred" compounds in *Chakrabarti 1980a*. Those five compounds are not a disclosed genus and each has either a fluorine or a hydroxyethyl group.

34. Only hindsight in light of Lilly's disclosures in the '382 patent would lead one with ordinary skill in the

art to recombine the components of the specific compounds discussed in *Chakrabarti 1980a* to create olanzapine. Under these circumstances, *Chakrabarti 1980a* does not anticipate the '382 patent. *Ruschig*, 343 F.2d at 974 ("We did not intend our *Petering* opinion or decision to become a precedent for the mechanistic dissection and recombination of the components of the specific illustrative compounds in every chemical reference containing them, to create hindsight anticipations with the guidance of an applicant's disclosures, on the theory that such reconstructed disclosures describe specific compounds within the meaning of section 102.").

35. Defendants have failed to prove by clear and convincing evidence that *Chakrabarti 1980a* anticipates any claim of the '382 patent. Findings of Fact § IV.A.1.

36. Moreover, Defendants have not shown by clear and convincing evidence that the uses, pharmaceutical compositions, and dosage ranges of claims 2, 3, 7, 8, and 15, are described in *Chakrabarti 1980a* as required by 35 U.S.C. § 102(b).

2. *Schauzu* Does Not Anticipate the Claims of the '382 Patent

37. DRL has failed to prove by clear and convincing evidence that the *Schauzu* publication anticipates any claim of the '382 patent. *Richardson*, 868 F.2d at 1236; *Celeritas*, 150 F.3d at 1361.

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38. The biological data in *Schauzu* comes from *Chakrabarti 1982*, which discloses only fluorinated piperazine compounds.

39. The structural formula in *Schauzu* does not comport with the biological data from *Chakrabarti 1982* as it is missing both (1) the fluorine atom that was in all the compounds for which the data was gathered, and (2) a nitrogen atom in what should have been a "piperazine" ring but which is actually drawn as a "piperidine" ring.

40. It is significant that neither *Chemical Abstracts* nor *Beilstein* abstracting services corrected the missing nitrogen atom. *E.I. DuPont De Nemours & Co. v. Ladd*, 117 U.S. App. D.C. 246, 328 F.2d 547, 552, 1964 Dec. Comm'r Pat. 337 (D.C. Cir. 1964) (holding that claimed compound not anticipated, and finding it significant that *Chemical Abstracts* did not mention the compound when abstracting the article alleged to disclose the compound). The fact that both abstracting services classified *Schauzu* as disclosing piperidines and that Zenith's expert, Dr. Reith, read *Schauzu* as referring to the fluorinated compounds of *Chakrabarti 1982*, supports the conclusion that *Schauzu* is at best ambiguous, and not anticipatory. *In re Brink*, 419 F.2d 914, 918, 57 C.C.P.A. 861 (C.C.P.A. 1970); *In re Turlay*, 304 F.2d 893, 899, 49 C.C.P.A. 1288, 1962 Dec. Comm'r Pat. 551 (C.C.P.A. 1962) ("It is well established that an anticipation rejection cannot be predicated on an ambiguous reference."); *In re Hughes*, 345 F.2d 184, 188, 52 C.C.P.A. 1355, 1965

Dec. Comm'r Pat. 598 (C.C.P.A. 1965) ("An ambiguous reference . . . will not support an anticipation rejection.").

41. To hold that *Schauzu* anticipates the '382 patent would require a person with ordinary skill in the art to mentally correct only the missing nitrogen atom while failing to correct the missing fluorine. DRL has not demonstrated why a skilled artisan would correct only one of those two errors. Thus, *Schauzu* cannot inherently anticipate. *Finnigan Corp. v. Int'l Trade Comm'n*, 180 F.3d 1354, 1365 (Fed. Cir. 1999) (The "mere possibility" that a skilled artisan would recognize and correct one error while leaving the other is "insufficient to show that it is inherently disclosed therein."). Findings of Fact § IV.A.2.

42. In addition, DRL has not shown by clear and convincing evidence that the uses, pharmaceutical compositions, and dosage ranges of claims 2, 3, 7, 8, and 15 are described in *Schauzu* as required by 35 U.S.C. § 102(b).

B. Obviousness

43. The nonobviousness requirement is set forth in 35 U.S.C. § 103(a) ("§ 103"), and reads:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject

> matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

44. Obviousness is a conclusion of law based on the following factual determinations: (1) the scope and content of the prior art, (2) the differences between the prior art and the claimed subject matter as a whole, (3) the level of skill in the art, and (4) where relevant, objective evidence of nonobviousness, i.e., the secondary considerations. *Graham v. John Deere Co.*, 383 U.S. 1, 17, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966); *see also Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1535-39, 1541 (Fed. Cir. 1983). The first three obviousness factors cited above comprise the prima facie case. *Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 1350 (Fed. Cir. 2000).

45. The claimed invention must be viewed "in the state of the art that existed at the time the invention was made.'" *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1050-51 (Fed. Cir. 1988) (quoting *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138 (Fed. Cir. 1985)).

46. "It is impermissible within the framework of section 103 to pick and choose from any one reference only

so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Wesslau*, 353 F.2d 238, 241, 53 C.C.P.A. 746 (C.C.P.A. 1965).

47. What a reference teaches is a question of fact addressed to a "person of ordinary skill in the art." *In re Bell*, 991 F.2d 781, 784 (Fed. Cir. 1993). The person of ordinary skill is an objective legal construct who is presumed to be aware of all the relevant prior art. *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 963 (Fed. Cir. 1986). This person is not deemed to be an innovator; rather, he is "presumed to think along the lines of conventional wisdom in the art." *Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985).

48. A proper obviousness analysis requires the recognition that the prior art, not hindsight knowledge of a patentee's success, must motivate a person skilled in the art to do what the patentee has done. *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1343 (Fed. Cir. 2000) (citing *In re Rouffet*, 149 F.3d 1350, 1357-58 (Fed. Cir. 1998)); *Grain Processing Corp. v. Am. Maize-Prods. Co.*, 840 F.2d 902, 907 (Fed. Cir. 1988) ("Care must be taken to avoid hindsight reconstruction by using the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.'")

(quoting *Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1012 (Fed. Cir. 1983)).

49. In the context of the structural similarity between the claimed chemical compound and the prior art chemical compounds, the prior art must give, *inter alia*, reason or motivation to make the claimed compound. *See In re Baird*, 16 F.3d 380 (Fed. Cir. 1994) (holding that obviousness had not been shown based on a single reference because the PTO had not demonstrated motivation to select claimed species from prior genus of millions of compounds); *see also In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (*en banc*) ("structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness . . .").

50. Where the prior art "teaches away" from the claimed invention rather than motivating a person of ordinary skill in the art to do what the patentee has done, the claimed invention is nonobvious. *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986); *W.L. Gore & Assocs. v. Garlock, Inc.*, 721 F.2d 1540, 1552-53 (Fed. Cir. 166 1983).

51. The prior art must also provide a reasonable expectation of success. *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1354 (Fed. Cir. 2003) ("A showing of

obviousness requires a motivation or suggestion to combine or modify prior art references, coupled with a reasonable expectation of success . . ."); *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). "Obvious to try" is not sufficient. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380 (Fed. Cir. 1986).

52. The assessment of obviousness also requires examination of objective evidence of nonobviousness. Such objective evidence, when present, must be considered and includes the extent of commercial success of the patented invention, unexpected properties of the invention compared to the prior art, whether the invention satisfies a long-felt need, whether others have failed to find a solution to the problem plaguing the art, and any copying of the invention by others. *Graham*, 383 U.S. at 17-18; *Stratoflex*, 713 F.2d at 1538-39, 1541.

53. Objective evidence is "often the most probative and cogent evidence in the record." *Stratoflex*, 713 F.2d at 1538. "It may often establish that an invention appearing to have been obvious in light of the prior art was not. It is to be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art." *Id.* at 1538-39.

54. Defendants have the burden of proof with respect to *all* of the obviousness factors, including, where relevant, objective evidence of nonobviousness. Specifically,

> the party asserting invalidity bears the initial burden of establishing a *prima facie* case of obviousness under 35 U.S.C. § 103. Once a *prima facie* case has been established, the burden shifts to the patentee to go forward with rebuttal evidence showing facts supporting nonobviousness. The party asserting invalidity, however, always retains the burden of persuasion on the issue of obviousness until a final judgment is rendered. Each fact forming the factual foundation upon which the court bases its ultimate conclusion regarding the obviousness of the claimed subject matter as a whole must be established by clear and convincing evidence.

Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 291-92 (Fed. Cir. 1985) (internal citations omitted); *see also Hybritech*, 802 F.2d at 1380 (objective evidence must be considered before a conclusion on obviousness is reached and is not merely "icing on the cake").

55. The weight to which the objective evidence is entitled depends on its nature and its relationship to the merits of the invention. *In re GPAC, Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995); *Ashland Oil*, 776 F.2d at 305 n.42.

56. "For objective evidence to be accorded substantial weight, its proponent must establish a nexus between

the evidence and the merits of the claimed invention." *GPAC*, 57 F.3d at 1580.

57. "The term nexus' is often used, in this context, to designate a legally and factually sufficient connection between the proven success and the patented invention, such that the objective evidence should be considered in the determination of nonobviousness." *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988).

1. The Prima Facie Case

58. Defendants contend that the prior art, including the '574 patent and *Chakrabarti 1980a*, would have motivated a person of ordinary skill to modify compound '222 or flumezapine to arrive at olanzapine.

59. As explained below, Defendants have not proven by clear and convincing evidence that the subject matter of any of claims 1, 2, 3, 7, 8, and 15 of the '382 patent would have been obvious within the meaning of § 103 to a person of ordinary skill in the art as of April 25, 1990.

a. It Would Not Have Been Obvious to Start with Compound '222

60. To prevail on the theory that olanzapine was an obvious modification of compound '222, Defendants must establish by clear and convincing evidence that

one of ordinary skill in the art would have been motivated to select compound '222 as a lead compound. *Yamanouchi*, 231 F.3d at 1344 ("Danbury did not show sufficient motivation for one of ordinary skill in the art at the time of invention to take [the step of] . . . selecting example 44 as a lead compound"); *see also Dillon*, 919 F.2d at 692 (finding that *prima facie* obviousness is established "where the prior art gives reason or motivation to make the claimed compositions").

61. Defendants have failed to meet that burden because the prior art would actually direct the person of ordinary skill in the art away from unfluorinated compounds like compound '222. The '574 patent (1) did not provide any biological data for compound '222, (2) suggested a preference for halogen-containing compounds, and (3) identified only a fluorine-containing compound, ethyl flumezapine, as "particularly active." Moreover, *Chakrabarti 1980a* (1) expressly taught that the addition of a fluorine or chlorine enhanced the activity and (2) indicated that the unfluorinated compound '222, there denominated compound 6, was less active than the benchmark compound, clozapine. Thus, rather then providing the requisite motivation, the prior art taught away from selecting compound '222 as a lead compound for further development.

62. If activity is the motivation for selecting the lead compound, other compounds which have been shown to be at least as active as clozapine would have been

the obvious choices to start with, not compound '222. *Yamanouchi*, 231 F.3d at 1345 ("If activity alone was the sole motivation, other more active compounds would have been the obvious choices."). Findings of Fact § IV.B.4.a.

b. It Would Not Have Been Obvious to Modify Compound 222 to Arrive at Olanzapine

63. Defendants have not shown any reason why one skilled in the art would have been motivated to select compound '222 as the lead compound except hindsight knowledge that its methyl analog (olanzapine) was later discovered by Lilly to be a successful, safe, atypical antipsychotic drug.

64. Defendants have also failed to prove by clear and convincing evidence that the prior art would have motivated a person of ordinary skill in the art to make the modification they propose. Nothing in the prior art would have motivated one of ordinary skill in the art to change the ethyl group in compound '222 to a methyl group to arrive at olanzapine. While the '574 patent and *Chakrabarti 1980a* stated a preference for short alkyl groups in the context of fluorinated compounds, the ethyl group on compound '222 is already such a group. There was no teaching that any one short alkyl group was better than any other short alkyl group. There was, therefore, no motivation to change one of these groups to another of these groups. There was no suggestion or reasonable expectation

of success in the prior art that changing an ethyl to a methyl would convert a compound having an inadequate activity profile into one having a desirable activity and safety profile. *See Dillon*, 919 F.2d at 692; Findings of Fact § IV.B.4.b.

c. It Would Not Have Been Obvious to Modify Flumezapine

65. Defendants have also failed to present clear and convincing evidence in support of their contention that it would have been obvious to modify the prior art by replacing the fluorine atom in flumezapine with a hydrogen atom to arrive at olanzapine. There is no motivation for making that change. *Yamanouchi*, 231 F.3d at 1343; *Dillon*, 919 F.2d at 692.

66. While the prior art taught that a fluorine atom might be acceptably replaced by a chlorine atom, it taught that replacing the fluorine atom with a hydrogen atom in a structurally similar compound would produce a compound having less activity than clozapine, the benchmark compound. In view of the necessity of maintaining activity, replacing the fluorine atom with a hydrogen atom would not have been the obvious choice. *W.L. Gore*, 721 F.2d at 1552-53.

67. Moreover, if elimination of toxicity is to be the motivation, Defendants have not proven by clear and convincing evidence that the prior art taught that the presence of the fluorine in flumezapine resulted in toxicity or that replacing the fluorine with hydrogen

would predictably eliminate any toxicity. Thus, there was no motivation to modify the prior art by replacing the fluorine atom in flumezapine with a hydrogen atom to arrive at olanzapine. Indeed, to the extent the prior art suggested possible sources of toxicity for flumezapine, it identified "hetero atoms" in the ring structure as the possible culprit, not the halogen atom. Findings of Fact § IV.B.4.c.

d. There Was No Reasonable Expectation of Success

68. Moreover, Defendants have failed to prove by clear and convincing evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in developing a safe, effective, atypical antipsychotic drug by making the changes to the prior art that they propose. *See Boehringer*, 320 F.3d at 1354; Findings of Fact § IV.B.5.

69. In this case, success was not simply finding a compound as active as clozapine in animal or *in vitro* tests that suggested possible efficacy. Others had achieved that result. Instead, success required an active compound without the adverse side effects of clozapine or other toxicities. *Yamanouchi*, 231 F.3d at 1345 ("success . . . was not discovering one of the tens of thousands of compounds that exhibit baseline [anti-ulcer] activity. Rather, the success was finding a compound that had high activity, few side effects, and lacked toxicity"); *Merck & Co. v. Teva Pharms. USA, Inc.*, 228 F.Supp. 2d 480, 503 (D. Del. 2002)

(considering nonobviousness of claimed compound with respect to side effects seen in prior art compounds), *aff'd*, 347 F.3d 1367 (Fed. Cir. 2003). Here, the ordinary medicinal chemist (or pharmacologist) would not have expected olanzapine to have the highly desirable combination of pharmacological properties that it possesses. The ordinary medicinal chemist would have had no reason to expect that olanzapine would have activity on par with clozapine, the benchmark compound, much less that it would have activity without the debilitating side effects of clozapine and other prior art compounds. Indeed, the long history of repeated failure to find a safe, atypical antipsychotic drug disposes of any allegation that freedom from unacceptable side effects could reasonably have been expected. *See* Findings of Fact § II.D.

70. Accordingly, the court finds Defendants have failed to establish a prima facie case of structural obviousness by clear and convincing evidence.

2. Objective Evidence of Nonobviousness — The Secondary Considerations

71. Even though Lilly has established its prima facie case, the court is required to examine the objective evidence of nonobviousness in the record. *Graham*, 383 U.S. at 17-18; *Stratoflex*, 713 F.2d at 1538-39, 1541. The secondary considerations include long-felt need, failure of others, commercial success, acclaim in the field, and unexpected results. *Ashland Oil*, 776 F.2d

at 291; *Corning Glass Works v. Sumitomo Elec. USA Inc.*, 671 F.Supp. 1369, 1398 (S.D.N.Y. 1987), *aff'd*, 868 F.2d 1251 (Fed. Cir. 1989).

a. Long-Felt Need

72. Evidence of a long-felt but unsolved need in the industry for the solution offered by the patented invention supports a finding that the invention would not have been obvious at the time the invention was made. *Monarch Knitting Machinery v. Sulzer Morat GmbH*, 139 F.3d 877, 884 (Fed. Cir. 1998); *see also* 35 U.S.C. § 103 ("A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious *at the time the invention was made* to a person of ordinary skill in the art.") (emphasis added).

73. "Long-felt need is analyzed as of the date of an articulated identified [sic] problem and evidence of efforts to solve that problem." *Texas Instruments v. United States ITC*, 988 F.2d 1165, 1178 (Fed. Cir. 1993).

74. The evidence reflects that there was a long-felt but unsolved need for a safe, atypical antipsychotic from 1975 until 1990.

75. In April of 1990, Lilly filed its patent application in the U.K.

76. Numerous investigators, including Lilly scientists, tried but failed to develop a safe, atypical antipsychotic.

77. Risperidone, an atypical antipsychotic, was first prescribed to schizophrenic patients in February 1994.

78. However, there is no record evidence which establishes when risperidone was invented or patented.

79. Therefore, the olanzapine patent application was filed well before risperidone was found to be safe and effective for use by schizophrenic patients. TX 1000.

80. Olanzapine satisfied the long-felt but unsolved need for a safe, atypical antipsychotic. Findings of Fact § IV.B.7.a.

b. Failure of Others

81. Evidence of failed attempts by others supports a finding that the patented invention would not have been obvious. *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1285 (Fed. Cir. 2000); *Minn. Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1574-75 (Fed. Cir. 1992) (reasoning competitors' failure to develop the patented invention suggested nonobviousness); *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 21 F.Supp.2d 366, 374 (S.D.N.Y. 1998) (stating that the evidence showing that "the pharmaceutical

industry at large was attempting to improve upon existing [anti-ulcer drugs] with only a small number of producers coming close to success" supports court's conclusion of nonobviousness).

82. The evidence establishes that there was a failure of others to develop a safe, atypical antipsychotic prior to the time Lilly filed its olanzapine patent application in the U.K. Findings of Fact § IV.B.7.b.

c. Commercial Success

83. Commercial success of an invention is evidence that the invention would not have been obvious. *Goodyear Tire & Rubber Co. v. Ray-O-Vac Co.*, 321 U.S. 275, 279, 88 L. Ed. 721, 64 S. Ct. 593, 1944 Dec. Comm'r Pat. 657 (1944); *Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573-74 (Fed. Cir. 1996).

84. A nexus between the claimed features of the invention and its commercial success is required. *Brown & Williamson Tobacco Corp. v. Phillip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000). "If the marketed product embodies the claimed features, and is coextensive with them, then a nexus is presumed and the burden shifts to the party asserting obviousness to present evidence to rebut the presumed nexus." *Id.*; *J.T. Eaton & Co. v. Atl. Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed. Cir. 1997) (stating that when the successful product is the invention disclosed and claimed in the patent, it is presumed that the

commercial success is due to the patented invention) (citing *Demaco*, 851 F.2d at 1392-93)).

85. In this case, the nexus is presumed because olanzapine embodies the claimed features and is coextensive with the claims of the '382 patent. The '382 patent claims the chemical compound olanzapine, its use to treat schizophrenia at doses below 20 mg/day, and pharmaceutical dosage forms containing those doses.

86. This presumption may be rebutted by evidence of substantial marketing or other promotional activity. *McNeil-PPC, Inc. v. L. Perrigo Co.*, 337 F.3d 1362, 1370 (Fed. Cir. 2003); *Brown & Williamson*, 229 F.3d at 1130; *J.T. Eaton & Co.*, 106 F.3d at 1571; *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996).

87. The evidence reflects that Lilly spent a substantial portion of its revenue on marketing and administrative costs.

88. As of 2001, olanzapine accounted for more than 25% of all antipsychotic prescriptions written; risperidone accounted for more than 29%.

89. As of 2001, olanzapine's overall U.S. sales totaled more than $ 2 billion.

90. The commercial success factor does not weigh in favor of Lilly or the Defendants. Findings of Fact § IV.B.7.c.

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d. Industry Acclaim

91. Appreciation of the invention by those of ordinary skill in the art is further evidence that the invention would not have been obvious. *E.g.*, *Vulcan Eng'g Co. v. Fata Aluminum, Inc.*, 278 F.3d 1366, 1373 (Fed. Cir. 2002); *In re Piasecki*, 745 F.2d 1468, 1473-74 (Fed. Cir. 1984); *Jenn-Air Corp. v. Modern Maid Co.*, 499 F.Supp. 320, 326-27 (D. Del. 1980), *aff'd*, 659 F.2d 1068 (3rd Cir. 1981).

92. The awards that Lilly received for the invention of olanzapine, including the Prix Galien Award in 1997, the Queen's Award for Enterprise in 2000, and the Pharmaceutical Manufacturer's Association Discoverers' Award in 2000, provide objective evidence of the nonobviousness of olanzapine. Testimonials from doctors and patients add further support for this finding.

93. Although the inventors of risperidone received the Prix Galien award in 1997, the court finds that olanzapine's industry acclaim is evidence of the nonobviousness of the '382 patent. Findings of Fact § IV.B.7.d.

e. Unexpected Results

94. Unexpected superior properties from an invention support the conclusion that the invention was not obvious to one of ordinary skill in the art. *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991);

In re De Blauwe, 736 F.2d 699, 705 (Fed. Cir. 1984). As the Federal Circuit has recognized, the reason behind this principle is "that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious." *In re Mayne*, 104 F.3d 1339, 1343 (Fed. Cir. 1997) (quoting *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995)).

95. In order for a showing of unexpected results to be probative of nonobviousness, such evidence must at least establish that: (1) there actually is a difference between the results obtained and those of the closest prior art, and (2) the difference actually obtained would not have been expected by one skilled in the art at the time of the invention. *In re Freeman*, 474 F.2d 1318, 1324 (C.C.P.A. 1973).

96. "When unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *Baxter Travenol Labs.*, 952 F.2d at 392.

97. Assessment of the obviousness of a chemical compound cannot, however, be based merely on comparisons between that compound's chemical structure and structures in the prior art. *In re Papesch*, 315 F.2d 381, 391, 50 C.C.P.A. 1084, 1963 Dec. Comm'r Pat. 334 (C.C.P.A. 1963). The law of § 103 also requires consideration of the respective biological and pharmacological properties of the claimed compound and those in the prior art before a final conclusion of obviousness can be reached. *Id.*

"There is no basis in law for ignoring any property in making a comparison of the claimed and prior art compounds." *In re Lunsford*, 327 F.2d 526, 528, 51 C.C.P.A. 1000, 1964 Dec. Comm'r Pat. 361 (C.C.P.A. 1964) (citing *Papesch*, 315 F.2d at 386-87, 391).

98. It is common practice in this field for pharmacologists, toxicologists, and regulators of the pharmaceutical industry to rely on animal test data to understand the biological properties of chemical compounds. Not surprisingly, therefore, the courts and the PTO, in evaluating unexpected differences in properties of pharmaceuticals in patent cases, have long accepted evidence from animal testing as objective evidence of nonobviousness. *E.g.*, *In re May*, 574 F.2d 1082, 1085 (C.C.P.A. 1978) (animal data, including toxicology data, accepted by the court as evidence of nonobviousness); *In re Blondel*, 499 F.2d 1311, 1315 (C.C.P.A. 1974) (tests in dogs showing unexpectedly superior duration of drug activity overcomes obviousness rejection); *In re Krazinski*, 347 F.2d 656, 662, 52 C.C.P.A. 1447, 1965 Dec. Comm'r Pat. 767 (C.C.P.A. 1965) (tests in mice used to overcome obviousness rejection); *United States v. Ciba-Geigy Corp.*, 508 F. Supp. 1157 (D.N.J. 1981) (drug nonobvious based on tests in animals), *see* 1164 (toxicity test in rats), 1168 (potency is an unexpected property), 1171 (potency tests in animals).

99. Evidence from pharmacological and toxicological testing in animals is accepted even though it is universally understood by those skilled in the art and

by the PTO that the results in animals indicate a potential for similar effects in humans, but cannot guarantee direct extrapolation. *In re Krimmel*, 292 F.2d 948, 953, 48 C.C.P.A. 1116, 1961 Dec. Comm'r Pat. 518 (C.C.P.A. 1961) (accepting animal tests to show practical utility notwithstanding the fact "that a demonstration that a compound has desirable or beneficial properties in the prevention, alleviation, or cure of some disease or manifestation of a disease in experimental animals does not necessarily mean that the compound will have the same properties when used with humans"); *see also In re Jolles*, 628 F.2d 1322, 1327 (C.C.P.A. 1980) ("It is clear that such testing [in experimental animals] is relevant to utility in humans.").

100. Evidence of unexpected results discovered after the patent issues are part of the obviousness inquiry. *See Richards on-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1482-83 (Fed. Cir. 1997) (finding that the court must consider all evidence of unexpected results, even that which it finds to have been unknown at the time of the invention); *In re Zenitz*, 333 F.2d 924, 927, 52 C.C.P.A. 746, 1964 Dec. Comm'r Pat. 878 (C.C.P.A. 1964); *Yamanouchi*, 21 F.Supp.2d at 370.

101. Olanzapine has several unexpectedly superior properties. Olanzapine has been found unexpectedly (1) not to produce the severe and widespread blood problems seen in dogs with ethyl flumezapine, (2) not to cause blood problems in humans of the sort seen with clozapine, and (3) not to cause a significant

elevation in average mean cholesterol seen in female dogs treated with compound '222.

102. Those differences in properties could not have been predicted from the structures of these molecules and are unexpected. They are strong evidence of nonobviousness. As applied to chemical compounds, a compound and all of its properties are inseparable and must be considered in determining obviousness. *See Papesch*, 315 F.2d at 391; Findings of Fact § IV.B.7.e.

3. Conclusion Regarding Obviousness

103. An analysis under *Graham*, supra., considering the scope and content of the prior art, the level of skill in the art, the differences between the prior art and olanzapine, and the objective evidence of nonobviousness, leads to the conclusion that Defendants have failed to prove by clear and convincing evidence that the subject matter claimed in any of claims 1, 2, 3, 7, 8, and 15 of the '382 patent would have been obvious within the meaning of 35 U.S.C. § 103 to a person of ordinary skill in the art as of April 25, 1990, the foreign priority filing date to which the '382 patent is entitled under 35 U.S.C. § 119.

Appendix B

C. Double Patenting

104. The defense of double patenting "precludes one person from obtaining more than one valid patent for either (a) the same invention,' or (b) an obvious' modification of the same invention." *In re Longi*, 759 F.2d 887, 892 (Fed. Cir. 1985).

105. The double-patenting law "prohibits the issuance of the claims in a second patent *not patentably distinct* from the claims of the first patent." *Id.*

106. Defendants must prove double patenting by clear and convincing evidence. *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1580 (Fed. Cir. 1991); *Carman Indus., Inc. v. Wahl*, 724 F.2d 932, 940 (Fed. Cir. 1983).

107. The first type of double patenting, based on the "same invention," arises from 35 U.S.C. § 101, which authorizes "*a* patent" to issue on an invention. Thus, same-invention or "statutory" double patenting prevents a second patent from issuing on an identical invention. *See Longi*, 759 F.2d at 892. Defendants do not advance an allegation of "same invention" double patenting in this case.

108. The second type of double patenting, sometimes referred to as "nonstatutory" or "obviousness type" double patenting, is based on federal common law rather than statute, and prevents a patent claim from validly issuing "when the claimed subject matter is

not patentably distinct from the subject matter claimed in a commonly owned patent." *In re Berg*, 140 F.3d 1428, 1431 (Fed. Cir. 1998).

109. A later claim is not patentably distinct if it "is obvious over, or anticipated by, the earlier claim." *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 968 (Fed. Cir. 2001). Thus, the court must determine whether "any claim in the application defines merely an obvious variation of an invention claimed in the patent asserted as supporting double patenting." *Gen. Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1278 (Fed. Cir. 1992) (citing *In re Vogel*, 422 F.2d 438, 57 C.C.P.A. 920, (C.C.P.A. 1970)); *accord Ortho Pharm. Corp. v. Smith*, 959 F.2d 936, 940 (Fed. Cir. 1992) (finding that double patenting precludes a second patent that "would have been obvious from the subject matter of the claims in the first patent, in light of the prior art") (quoting *Longi*, 759 F.2d at 893). "If the rejected claim defines *more* than an obvious variation, it is *patentably distinct*." *Gen. Foods*, 972 F.2d at 1278 (emphasis in original).

110. "The fundamental reason for the rule [of obvious-type double patenting] is to prevent unjustified timewise extension of the right to exclude granted by a patent no matter how the extension is brought about." *Eli Lilly & Co.*, 251 F.3d at 968 (quoting *In re Van Ornum*, 686 F.2d 937, 943-44 (C.C.P.A. 1982)).

111. The double patenting analysis involves a two-step process. First, the court must determine the

differences between the claims of the patents. Second, the court must determine whether the differences in the claimed subject matter between the earlier and later patents render the claims patentably indistinct or obvious. *Eli Lilly & Co.*, 251 F.3d at 967-68.

1. Domination

112. Defendants argue that because the '382 patent claims a particular species of the enormous genus of chemical compounds claimed in the '574 patent, the '382 patent is invalid for double patenting.

113. Domination in patent law is a situation in which one patent has a broad, or generic, claim which embraces the subject matter claimed in a later, and narrower, patent. The first patent therefore "dominates" the latter "because the more narrowly claimed invention cannot be practiced without infringing the broader claim." *In re Kaplan*, 789 F.2d 1574, 1577 (Fed. Cir. 1986). "This commonplace situation is not, per se, double patenting." *Id.* at 1577-78.

114. So long as the later patent meets all of the requirements of patentablity, including novelty and nonobviousness, it can properly coexist with the earlier-expiring dominant patent, and "domination is an irrelevant fact." *Id.* at 1578.

115. Although the doctrine of double patenting prevents "unjustified timewise extension of the right to exclude granted by a patent," *Eli Lilly & Co.*, 251 F.3d at 968,

there is no unjustified extension when the patented improvement invention is not obvious. *In re Braat*, 937 F.2d 589, 594-95 (Fed. Cir. 1991) ("Only if the extension of patent right is *unjustified* is a double patenting rejection appropriate. There are situations where the extension is justified. This case presents such a situation.") (emphasis in original).

116. In this case, the '382 patent is not obvious. *See generally*, Findings of Fact § IV.B.

2. The Double Patenting Issue

117. The double patenting issue presented in this case is whether the subject matter of the '382 patent claims would have been obvious from the *claims* of the '574 patent. Because under 35 U.S.C. § 103 the narrower selection invention claimed in the '382 patent would not have been obvious from the entire text of the '574 patent, that invention similarly would not have been obvious from the claims of the '574 patent as a matter of law. *See* Findings of Fact § IV.B.1.b. The similarity of the analysis, as well as the findings and conclusions relating to the novelty and nonobviousness of the '382 patent claims in light of the '574 patent, are equally relevant to the issue of nonstatutory double patenting.

118. Where the reference patent is prior art, as in this case, the analysis for obviousness-type double patenting and obviousness under § 103 certainly begin in the same way. *See In re Land*, 368 F.2d 866, 884, 54 C.C.P.A. 806 (C.C.P.A. 1966); *see also In re Jezl*,

396 F.2d 1009, 1013, 55 C.C.P.A. 1234 (C.C.P.A. 1968) ("The view we take renders it unnecessary to consider at length the double patenting rejection advanced by the [PTO]. That rejection — one of double patenting of the obvious type' — presents the same basic question as the § 103 rejection, but in narrower aspect."); *In re Ornitz*, 376 F.2d 330, 334, 54 C.C.P.A. 1304 (C.C.P.A. 1967) ("Where it is possible to conduct the broader inquiry permitted by sections 102(e) and 103 because the references are prior art,' it does not make sense to resort to the narrower inquiry which underlies a double patenting' rejection."); *Ex parte Yokogawa*, No. 95-2830, 1999 WL 33220561, at *2 (PTO Bd. Pat. App. & Int. 1999) ("In the case before us, the underlying U.S. Patent 5,478,936 constitutes prior art . . . Accordingly, we will consider the obvious-type double patenting rejection . . . as having been subsumed by the rejection of the claims under 35 U.S.C. § 103 over the same reference.") (citing *Ornitz*, 376 F.2d at 334; *In re Bowers*, 359 F.2d 886, 891 n.7, 53 C.C.P.A. 1590 (C.C.P.A. 1966)).

119. In this regard, the PTO itself has long recognized that the obvious-type double-patenting analysis parallels the obviousness analysis under *Graham*. "The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1996), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103 are employed when making an obvious-type double patenting analysis," including "objective indicia of

nonobviousness." Manual of Patent Examining Procedure § 804(II)(B)(1) (Aug. 2000). Accordingly, Defendants have not proven by clear and convincing evidence that claims 1, 2, 3, 7, 8, or 15 of the '382 patent are invalid for obviousness-type double patenting. Findings of Fact § IV.C.

120. The Federal Circuit's recent decision in *Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1377-78 (Fed. Cir. 2003), does not require a contrary result. Defendants rely upon a footnote in that case where the Federal Circuit stated that nonstatutory double patenting (as opposed to obviousness under § 103) does not require inquiry into the motivation to modify the prior art or into objective evidence of nonobviousness. *Id.* at 1377 n.1.

121. The court agrees with Lilly's interpretation of *Geneva Pharm.* as a case involving nonstatutory double patenting based upon anticipation under § 102 rather than obviousness under § 103. *Id.* at 1384 ("This genus-species relationship makes the claims patentably indistinct, because the earlier species within the Crowley claim anticipates the later genus of the 352 and 552 claims."). This interpretation makes sense in view of the law of anticipation, which does not require evidence of motivation to modify and objective evidence of nonobviousness. *E.g., In re Paulsen*, 30 F.3d 1475, 1482 n.11 (Fed. Cir. 1994) ("Evidence of nonobviousness is irrelevant for patentability purposes when an invention is anticipated under section 102."). Thus, *Geneva*

Pharm. is inapplicable to the double patenting issue raised in this case.

122. Prior cases also support Lilly's reading of *Geneva Pharm.* Specifically, cases dealing with the other form of nonstatutory double patenting, involving obviousness, demonstrate that the issues of motivation and objective evidence of nonobviousness are relevant and must be considered. *Ortho Pharm.*, 959 F.2d at 943 ("Given the structure and properties of the components claimed in 081 and 909, there would have been no suggestion in the art (and, hence, it would not have been obvious) to modify those structures in order to achieve the compounds of [the patent-in-suit]."); *see also In re Baird*, 348 F.2d 974, 979, 52 C.C.P.A. 1747, 1965 Dec. Comm'r Pat. 1072 (C.C.P.A. 1965) ("This [double-patenting] problem may also be stated to be whether it would have been obvious to one of ordinary skill to modify the process of the patent claims by eliminating the irradiation step."); *In re Emert*, 124 F.3d 1458, 1462 (Fed. Cir. 1997) ("Absent some indication of unexpected properties, the [patented] combination rendered [the claimed invention] obvious [for double patenting]."); *Longi*, 759 F.2d at 896 ("We must look to the Albizatti declaration [purporting to outline unexpected results] to determine whether the Board correctly concluded that this sole rebuttal evidence was insufficient to overcome the *prima facie* case.").

Appendix B

D. Public Use

123. 35 U.S.C. § 102 provides that a person is entitled to a patent unless

> (b) the invention was . . . in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States.

124. To establish a prima facie case of public use, the party asserting the bar must show the following factors by clear and convincing evidence: (1) the invention was used in public more than a year before the patent filing date and (2) the use was "without restriction, and in circumstances other than substantially for the purposes of experiment.'" *Allied Colloids Inc. v. Am. Cyanamid Co.*, 64 F.3d 1570, 1574 (Fed. Cir. 1995) (quoting *Smith & Griggs Mfg. Co. v. Sprague*, 123 U.S. 249, 256, 31 L. Ed. 141, 8 S. Ct. 122, 1887 Dec. Comm'r Pat. 616 (1887)); *Tone Bros., Inc. v. Sysco Corp.*, 28 F.3d 1192, 1197 n.4 (Fed. Cir. 1994). Once that burden is met, the patent owner has the burden of coming forward with convincing evidence to counter the prima facie case. The burden of persuasion, however, always remains with the party asserting the bar. *Tone*, 28 F.3d at 1197 n.4; *TP Labs.*, 724 F.2d at 971.

125. Whether an activity constitutes an invalidating "public use" is a question of law based on underlying

factual findings. *Minn. Mining & Mfg.*, 303 F.3d at 1301.

126. One public use is enough to invalidate a patent. *Egbert v. Lippmann*, 104 U.S. (14 Otto) 333, 336, 14 Otto 333, 26 L. Ed. 755, 1882 Dec. Comm'r Pat. 35 (1881); *Electric Storage Battery Co. v. Shimadzu*, 307 U.S. 5, 19-20, 83 L. Ed. 1071, 59 S. Ct. 675, 1939 Dec. Comm'r Pat. 870 (1939).

1. The HGAA, HGAB, and HGAC Phase I Clinical Trials Were Not a Public Use of Olanzapine

127. Defendants have failed to prove by clear and convincing evidence that the HGAA, HGAB, and HGAC Phase I clinical trials of olanzapine were public. These studies were conducted by Lilly personnel in the Lilly clinic. Lilly restricted access to the facility and provided full-time security. In addition, the studies were fully controlled by Lilly. The volunteers, who were healthy and not suffering from schizophrenia, were paid by Lilly for their services, remained in the research ward for the duration of the study, and were closely monitored by doctors and medical staff employed by Lilly. Only Lilly employees administered the drug. The fact that the volunteers were allowed visitors does not change the analysis. *See e.g.*, *Bergstrom v. Sears, Roebuck & Co.*, 457 F. Supp. 213, 220 (D. Minn. 1978), *aff'd*, 599 F.2d 62 (8th Cir. 1979) (finding that the presence of casual visitors did not create a public use).

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128. Defendants' argument that the clinical trials were "public" because the patients did not sign a confidentiality agreement is unpersuasive and legally unsound. First, because the patients were not informed of the identity of the compound they were taking and were kept at Lilly facilities at all times, a confidentiality agreement would have been superfluous. Second, the presence or absence of a confidentiality agreement is not controlling. It is simply one of many factors to be taken into consideration. *See Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1266 (Fed. Cir. 1986) (citing *TP Labs.*, 724 F.2d at 972).

129. Defendants' reliance on *Egbert v. Lippman*, 104 U.S. 333 (1881), is misplaced. In that case, the inventor made and gave his invention to a friend who used the invention for eleven years before the inventor obtained a patent. In addition, three years before he obtained a patent, the inventor showed another witness the invention, also in use by the inventor's wife at that time, and explained to that witness how the invention functioned. *Id.* at 335. The Court found the inventor presented the invention to his friend for her use in public by his consent and allowance without any obligation of secrecy or restriction at all. *Id.* at 337. These facts differ markedly from the facts in the present case.

130. Given the totality of the circumstances, the Phase I clinical trials do not constitute a public use under § 102(b). Findings of Fact § IV.D.

2. The HGAA, HGAB, and HGAC Phase I Clinical Trials Were Not a "Use" of the Claimed Invention

131. The sole disclosed utility for olanzapine in the '382 patent is to treat disorders of the central nervous system. That utility is clearly reflected, for example, in patent claims 7 and 8, which claim methods of treating a person suffering from or susceptible to schizophrenia.

132. The subjects of the Phase I clinical trials were normal volunteers who were not suffering from any disorder of the central nervous system and who were not receiving olanzapine for any pharmaceutical or medicinal purpose whatsoever. These were safety experiments. They were not "public uses" of the pharmaceutical invention claimed in the '382 patent. *See* Findings of Fact § IV.D.

3. The HGAA, HGAB, and HGAC Phase I Clinical Trials Were "Experimental Uses" of Olanzapine

133. Even if the court had found that Lilly's Phase I clinical trials of olanzapine constituted a public use of the compound more than one year prior to Lilly's application for its patent, Defendants have failed to prove by clear and convincing evidence that it was not an experimental use.

134. The public use bar has always been tempered by an inventor's right to test his invention, even in public, in order to determine that it is operable for its intended purpose. *City of Elizabeth v. Am. Nicholson Pavement Co.*, 97 U.S. 126, 24 L. Ed. 1000 (1877) (finding that the fact that his invention, a type of pavement, was laid down as a test more than six years before the patent application was not an invalidating public use because the use was a "bona fide effort to bring his invention to perfection, or to ascertain whether it will answer the purpose intended."). This is referred to as an "experimental use" and it "negates" what might otherwise appear to have been a public use. *See TP Labs.*, 724 F.2d at 971.

135. Once an invention is reduced to practice, further testing will not qualify as experimental use for purposes of the experimental use negation under § 102(b). *EZ Dock v. Schafer Sys., Inc.*, 276 F.3d 1347, 1352 (Fed. Cir. 2002); *Cont'l Plastic v. Owens Brockway Plastic Products, Inc.*, 141 F.3d 1073, 1079 (Fed. Cir. 1998). "In order to establish an actual reduction to practice, the inventor must prove that . . . the invention will work for its intended purpose." *Taskett v. Dentlinger*, 344 F.3d 1337, 1340 (Fed. Cir. 2003).

136. "Determining whether an invention will work for its intended purpose may require testing, depending on the character of the invention and the problem it solves." *Slip Track Sys., Inc. v. Metal-Lite, Inc.*, 304

F.3d 1256, 1265 (Fed. Cir. 2002) (citing *Cooper v. Goldfarb*, 154 F.3d 1321, 1327 (Fed. Cir. 1998)).

137. The evidence demonstrates that the art with respect to this type of atypical antipsychotic drug was highly unpredictable. Small structural changes led to very different properties. Furthermore, the art was plagued with unpredicted side effects that rendered otherwise promising compounds useless in the clinical setting. These side effects could only be understood when the compounds were tested in actual patients. Olanzapine was conceived as a compound that would have antipsychotic iactivity but not produce flumezapine's toxic effects in schizophrenic patients. Accordingly, testing olanzapine in actual schizophrenic patients was required to prove it would "work for its intended purpose," i.e., as a safe, atypical antipsychotic drug used to treat human patients suffering from or susceptible to psychotic disorders. These Phase I clinical trials in healthy human volunteers were required by regulatory agencies before the compound could be tested in schizophrenic patients. Paul Tr. 132:12-134:11; Goldberg Tr. 308:9-15.

138. For these reasons, the clinical tests constitute an experimental use and negate a finding that they were a "public use" as defined in patent law. Findings of Fact § IV.D.

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E. Inequitable Conduct

139. Patent applicants are required to prosecute patent applications with candor, good faith, and honesty. *Semiconductor Energy Lab. Co. v. Samsung Electronics Co.*, 204 F.3d 1368, 1373 (Fed. Cir. 2000).

140. Attorneys, agents, and applicants who have applications pending before the PTO have an uncompromising duty to report all facts concerning possible fraud or inequitable conduct underlying the application. *See Precision Instrument Mfg. Co. v. Automotive Maintenance Mach. Co.*, 324 U.S. 806, 818, 89 L. Ed. 1381, 65 S. Ct. 993, 1945 Dec. Comm'r Pat. 582 (1945).

141. If a patent applicant violates these duties, the patent may be held unenforceable due to inequitable conduct. *See Bristol-Myers Squibb Co. v. Rhone-Poulenc Rorer, Inc.*, 326 F.3d 1226, 1233 (Fed. Cir. 2003).

142. "Inequitable conduct includes affirmative misrepresentation of a material fact, failure to disclose material information, or submission of false material information, coupled with an intent to deceive." *Semiconductor Energy Lab.*, 204 F.3d at 1373.

143. The duty of candor extends throughout the patent's entire prosecution history. *Fox Indus. v. Structural Preservation Sys., Inc.*, 922 F.2d 801, 803 (Fed. Cir. 1990).

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144. Inequitable conduct requires Defendants to prove the elements by clear and convincing evidence. *Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544, 551 (Fed. Cir. 1990).

145. "Inequitable conduct entails a two-step analysis: first, a determination of whether the withheld reference meets a threshold level of materiality and intent to mislead, and second, a weighing of the materiality and intent in light of all the circumstances to determine whether the applicant's conduct is so culpable that the patent should be unenforceable." *GFI, Inc. v. Franklin Corp.*, 265 F.3d 1268, 1273 (Fed. Cir. 2001); *see also Hoffmann-La Roche, Inc. v. Promega Corp.*, 323 F.3d 1354, 1359 (Fed. Cir. 2003).

146. Thus, to prevail on their inequitable conduct allegations, Defendants must prove that the prior art or other information that has allegedly been withheld or misrepresented was material to patentability. They must then demonstrate knowledge, chargeable to those responsible for prosecuting the application, of that information and of its materiality. Finally, they must prove that an individual (not "Lilly" generally) having a duty of disclosure to the PTO intentionally withheld or misrepresented the information with an intent to mislead the PTO. *FMC Corp. v. Manitowoc Co.*, 835 F.2d 1411, 1415 (Fed. Cir. 1987).

Appendix B

1. Materiality

147. The duty of disclosure is codified in the regulations governing patent application proceedings before the PTO. 37 C.F.R. § 1.56 (1992) ("Rule 56"). Regulations consistent with statutes have the force and effect of law. *Wyden v. Comm'r of Patents & Trademarks*, 807 F.2d 934, 935-36 (Fed. Cir. 1986) (*en banc*) ("The Commissioner's promulgation of regulations, which are found in 37 C.F.R., . . . if not inconsistent with law, . . . have the force and effect of law."); *Norton v. Curtiss*, 433 F.2d 779, 791, 57 C.C.P.A. 1384 (C.C.P.A. 1970) ("[Title] 35 U.S.C. § 6 [now § 2(b)(2)(A)] . . . gives the Commissioner authority to establish regulations governing the conduct of proceedings in the Patent Office. We have long held that such regulations, when not inconsistent with the statutes, have the force and effect of law.").

148. Prior to 1992, Rule 56 defined information as being material "where there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent." 37 C.F.R. § 1.56 (1990).

149. The PTO amended Rule 56 in March 1992 "to address criticism concerning a perceived lack of certainty in the materiality standard." 57 Fed. Reg. 2021, 2023 (Jan. 17, 1992). The revised rule applied to applications that were pending in March 1992 and thereafter. *Id.* Because the '382 patent was pending in March 1992 (it did not issue until 1993), the revised

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Rule 56 governs the duty of disclosure in the present case. *Baxter Int'l, Inc. v. McGaw, Inc.*, 149 F.3d 1321, 1328 n.3 (Fed. Cir. 1998); *Critikon, Inc. v. Becton Dickinson Vascular Access, Inc.*, 120 F.3d 1253, 1256 (Fed. Cir. 1997).

150. As revised in 1992, Rule 56 provides that information is material to patentability only when it is "not cumulative to information already of record or being made of record in the application" and either "establishes . . . a prima facie case of unpatentability of a claim" or "refutes, or is inconsistent with a position the applicant takes." 37 C.F.R. § 1.56(b) (1992). A reference is said to be cumulative if it "teaches no more than what a reasonable examiner would consider to be taught by the prior art already before the PTO." *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1575 (Fed. Cir. 1997).

151. This change "was not intended to constitute a significant substantive break with the previous standard." *Hoffmann-La Roche, Inc.*, 323 F.3d at 1368 n.2 (citing 57 Fed. Reg. 2021, 2023 (Jan. 17, 1992).

2. Intent to Deceive

152. In *Kingsdown Medical Consultants, Ltd. v. Hollister, Inc.*, 863 F.2d 867 (Fed. Cir. 1988) (*en banc* in relevant part), the Federal Circuit held that an actual intent to deceive is a required element. A good-faith error in judgment, a mistake, negligence, or even grossly negligent failures are not sufficient to render

an otherwise valid patent unenforceable. *Id. at* 876 ("[A] finding that particular conduct amounts to gross negligence' does not of itself justify an inference of intent to deceive; the involved conduct, viewed in light of all the evidence, including evidence indicative of good faith, must indicate sufficient culpability to require a finding of intent to deceive.").

153. "Intent [to deceive] need not be proven by direct evidence; it is most often proven by a showing of acts, the natural consequences of which are presumably intended by the actor." *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1180 (Fed. Cir. 1995).

154. "Generally, intent must be inferred from the facts and circumstances surrounding the applicant's conduct." *Id.* at 1180-81.

155. "Although there may be special circumstances in which intent is appropriately deemed established by inference alone, there must be sufficient evidence to support such inference." *Hupp v. Siroflex of Am., Inc.*, 122 F.3d 1456, 1466 (Fed. Cir. 1997); *see also Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1482 (Fed. Cir. 1998) ("Inference without any probative evidence is insufficient to show culpable intent.").

156. In ascertaining an applicant's intent, the court must consider the totality of the circumstances. *Baxter Int'l*, 149 F.3d at 1330 ("It is the totality of the applicant's

conduct that creates the inference upon which the applicant's intent can be ascertained.").

157. The required intent cannot be proven by evidence of materiality alone. "Inequitable conduct requires an intent to act inequitably. Materiality of an undisclosed reference does not presume an intent to deceive." *Halliburton Co. v. Schlumberger Tech. Corp.* 925 F.2d 1435, 1442 (Fed. Cir. 1991). "Intent is an independent element of inequitable conduct . . . and must be separately established." *Hupp*, 122 F.3d at 1465; *accord Allen Organ Co. v. Kimball Int'l, Inc.*, 839 F.2d 1556, 1567 (Fed. Cir. 1988) ("Absent intent to withhold[,] it is not controlling whether the reference is found to anticipate or otherwise to be material.").

158. However, "the more material the conduct, the less evidence of intent will be required in order to find that inequitable conduct has occurred." *PerSeptive Biosystems, Inc. v. Pharmacia Biotech, Inc.*, 225 F.3d 1315, 1319 (Fed. Cir. 2000).

159. A showing of subjective good faith militates against a finding of intent to deceive. *Kingsdown*, 863 F.2d at 876; *Hoffman-La Roche Inc. v. Lemmon Co.*, 906 F.2d 684, 688 (Fed. Cir. 1990).

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3. Lilly Did Not Commit Inequitable Conduct During the Prosecution of the '382 Patent

160. Defendants have failed to prove by clear and convincing evidence that anyone associated with the prosecution of the '382 patent misrepresented or concealed material prior art or other information with an intent to deceive the PTO.

a. Lilly's Nondisclosure of Prior Art Does Not Constitute Inequitable Conduct

161. *Chakrabarti 1980a* and the '574 patent were not disclosed as prior art to the Examiner during the prosecution of the '382 patent.

162. PTO procedure allows a patent applicant to file an information disclosure statement at any time before the PTO closes the prosecution of the application. 37 C.F.R. § 1.97(c). An applicant who fails to disclose prior art cannot be said to have acted inequitably when the information was, in fact, considered by the PTO. *Molins PLC*, 48 F.3d at 1185 (citing *Scripps*, 927 F.2d at 1582); *Orthopedic Equip. Co. v. All Orthopedic Appliances, Inc.*, 707 F.2d 1376, 1383-84 (Fed. Cir. 1983) ("The nondisclosure was not found to be material; rather, the district court found that the examiner assigned to prosecution of the patent-in-suit independently ascertained the existence of the undisclosed prior art. [Defendant] has not shown the underlying findings of fact to be clearly erroneous.").

163. Furthermore, PTO regulations state that "the duty to disclose all information known to be material to patentability is deemed to be satisfied if all information known to be material to patentability of any claim issued in a patent *was cited by the Office* or submitted to the Office . . ." 37 C.F.R. § 1.56(a) (emphasis added).

164. *A.B. Dick Co. v. Burroughs Corp.*, 798 F.2d 1392 (Fed. Cir. 1986), upon which Defendants rely, was decided before the promulgation of the 1992 amendment to the PTO rules (which made it clear that the duty of disclosure does not extend to documents cited by the PTO), before the Federal Circuit's decision in *Kingsdown* (which made it clear that gross negligence was not sufficient to support a finding of inequitable conduct), and involved a unique factual scenario not present here. In *A.B. Dick*, the PTO completed its examination of the application, indicated it was allowable, and instituted a patent interference with respect to it before discovering a highly material reference that the applicant had been aware of throughout the prosecution. *Id.* at 1394-96. In the present case, the prior art was cited and considered by the PTO in making its very first Office Action rejecting the claims of the olanzapine patent application.

165. Therefore, Lilly's failure to disclose *Chakrabarti 1980a* and the '574 patent to the Examiner during the prosecution of the '382 patent was not a material omission. *See* 37 C.F.R. § 1.56(a).

166. Moreover, Defendants have not proven by clear and convincing evidence that Lilly concealed *Chakrabarti 1980a* or the '574 patent with an intent to deceive the PTO. Findings of Fact § IV.E.18.a.

167. Lilly also failed to disclose *Chakrabarti 1982* and *Chakrabarti 1989* to the PTO as prior art.

168. *Chakrabarti 1982* and *Chakrabarti 1989* were cumulative to other information the PTO considered; therefore, these prior art references were not material to the PTO's decision regarding the patentability of olanzapine. *See* 37 C.F.R. § 1.56(b); Findings of Fact § IV.E.18.b.

169. Further, Defendants have not proven by clear and convincing evidence that anyone at Lilly concealed *Chakrabarti 1982* and *Chakrabarti 1989* with the intent to deceive the PTO. Findings of Fact § IV.E.18.b.

b. Dr. McGrath Believed the Cholesterol Results of the D07290 Study Were Significant

170. Lilly's initial claims of unexpected differences were made based upon the reported findings of Dr. McGrath, the clinical pathologist assigned to the D07290 Study, and not upon the findings of Dr. Symanowski.

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171. Dr. McGrath believed the cholesterol results seen in the D07290 Study were biologically significant at the time he reported his results to Lilly and before Lilly filed the olanzapine patent application.

172. Accordingly, Defendants have not proven by clear and convincing evidence that Dr. McGrath believed the results were not significant before Lilly filed the olanzapine patent application and that his views were intentionally withheld from the PTO with an intent to deceive. Findings of Fact § IV.E.3.

173. The court further finds that Lilly properly corrected the definition of "clinical pathological significance." Dr. McGrath testified that his original definition did not reflect the actual evaluation of the data. Dr. McGrath decided to amend the definition in the interest of clarity and conformity. The final report submitted to the FDA in May 1995 reflected the correct definition.

174. Accordingly, there is no clear and convincing evidence that in presenting the data to the PTO, anyone at Lilly intended to deceive the PTO or materially misrepresented factual data. Findings of Fact § IV.E.4.

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c. Dr. Symanowski Did Not Conceal or Misrepresent the D07290 Study Data

(1) The Use of the Repeated Measures Analysis

175. Dr. Symanowski analyzed the data from the D07290 Study using the repeated measures analysis of variance, a sound statistical method that he believed to be the correct method of analysis given the purpose of the D07290 Study.

176. Dr. Symanowski did not inform the PTO that he changed the statistical analysis from Dunnett's test as disclosed in the D07290 Dog Study protocol because he did not believe that it was necessary to inform the PTO of an incorrect methodology.

177. Defendants failed to prove by clear and convincing evidence that Dr. Symanowski's decision to use the repeated measures analysis over the Dunnett's test, and his failure to inform the PTO of that change in protocol, resulted in an affirmative misrepresentation of material fact, or a material omission of fact. In addition, Defendants failed to prove by clear and convincing evidence that Dr. Symanowski acted with an intent to deceive the PTO regarding the results of the D07290 Study. *See Semiconductor Energy Lab.*, 204 F.3d at 1373 ("Inequitable conduct includes affirmative misrepresentation of a material fact, failure to disclose material information, or submission of false material information, coupled with an intent

to deceive.") (quoting *Molins PLC*, 48 F.3d at 1178); Findings of Fact § IV.E.12.

(2) The Failure to Include Individual Dog Data

178. Dr. Symanowski did not include the plots of the individual dog data in his declaration to the PTO.

179. The purpose in generating the individual plots of the dog data was to look for and identify outliers and to gain confidence in his statistical analysis.

180. There is no evidence that the individual dog data was not consistent with the mean data Dr. Symanowski reported to the PTO.

181. Defendants failed to prove by clear and convincing evidence that Dr. Symanowski's failure to include the individual dog data was materially misleading or done with an intent to deceive the PTO. Findings of Fact § IV.E.7.

(3) The Failure to Include Nonprotocol Bleed Data

182. Dr. Symanowski did not include nonprotocol bleed data of Dog 240712 and Dog 240692, two of the high-dose olanzapine-treated female dogs, because the inclusion of such data would improperly introduce bias into the D07290 Study results.

183. Dr. Thisted and Dr. Gibbons testified that they analyzed all of the data points, including the protocol and nonprotocol bleed data, and found that the results were still statistically significant.

184. There is no clear and convincing evidence that Dr. Symanowski, or anyone associated with Lilly, withheld these nonprotocol bleed measurements with an intent to deceive the PTO. Findings of Fact § IV.E.8.

(4) The Failure to Inform the PTO of the Results of the Robustness Check

185. Dr. Symanowski performed a "robustness check" to confirm the results of his final analysis of the D07290 Study data, but he did not disclose his findings to the PTO because it was not customary to do so.

186. Defendants failed to prove by clear and convincing evidence that Dr. Symanowski's failure to include the results of the robustness checks to the PTO was a material omission or that he intended to deceive the PTO. Findings of Fact § IV.E.13.

(5) Figure 3 of Dr. Symanowski's Declaration

187. Figure 3 of Dr. Symanowski's declaration depicts the mean cholesterol concentrations of female dogs from three groups — the control group, the 8 mg/kg/day

olanzapine group, and the 8 mg/kg/day compound '222 group, plus or minus one standard error.

188. Dr. Symanowski's use of the standard error over the standard deviation is not materially misleading. Indeed, the standard deviation can be calculated from the standard error by a simple mathematical calculation. *See* 37 C.F.R. § 1.56(b).

189. Defendants failed to prove by clear and convincing evidence that Dr. Symanowski's graph, depicted in Figure 3 of his declaration, was materially misleading or was submitted with the intent to mislead the PTO. Findings of Fact § IV.E.14.

(6) The Failure to Disclose the Results of Other Parameters

190. Dr. Symanowski found other statistically significant increases in certain parameters with respect to male dogs given 8 mg/kg/day of olanzapine compared to male dogs given 8 mg/kg/day of compound '222 and control males in the D07290 Study. These include erythrocytic parameters (erythrocyte count, hemoglobin concentration, and packed cell volume), bilirubin, and albumin.

191. Dr. Symanowski did not report these results to the PTO.

192. Dr. McGrath determined that these findings, while statistically significant, were not biologically significant.

193. In reliance on the information Dr. Means received from Dr. McGrath, Dr. Means reported to the PTO that the changes in these parameters had "slightly increased" in the male dogs given 8 mg/kg/day of olanzapine.

194. Defendants failed to prove by clear and convincing evidence that anyone at Lilly believed the increase in erythrocytic parameters, bilirubin, and albumin were biologically significant and thus material to patentability. Therefore, Dr. Symanowski's failure to disclose the statistically significant changes in these parameters was not a material omission of fact made with an intent to deceive the PTO. Defendants also failed to prove by clear and convincing evidence that Dr. McGrath's description of the statistically significant change observed in these parameters as "slight" was intended to deceive the PTO. *See* 37 C.F.R. § 1.56(b); Findings of Fact § IV.E.15.

d. Statements Made by Other Lilly Representatives Do Not Constitute Inequitable Conduct

(1) Lilly's Response to the Swedish Board of Health

195. When Lilly sought to conduct human clinical studies of olanzapine, the Swedish Board of Health required Lilly to respond to concerns it had about the hematotoxicity of olanzapine seen in dogs treated with 10 mg/kg/day.

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196. In its Response, Lilly discounted the effects of olanzapine on grounds that the dosage administered to the test animals was at large multiples of the clinical dose.

197. The declarations of Dr. Means and Dr. Emmerson did not inform the PTO that the results of the D07290 Study should be discounted as the negative cholesterol effects seen in the compound '222-treated female dogs were similarly seen at large doses.

198. The failure to apprise the PTO of this information is not a material omission. The Response to the Swedish Board addressed many factors that accounted for the blood toxicity readings in the test animals. The dosage was only one of the factors.

199. Thus, Lilly's Response to the Swedish Board of Health does not constitute clear and convincing evidence that Lilly believed the results of the D07290 Study should be discounted merely because the results were seen only in the high-dose female dogs. Findings of Fact § IV.E.1.

200. Moreover, the fact that Lilly's submission to the Swedish Board of Health compared the effects of olanzapine in multiple species does not discount the results of the D07290 Study. It was not necessary to test compound '222 in a second species, as the negative results seen in the female high-dose compound '222-treated dogs were sufficient for one

to reasonably assume that such results would also occur in humans.

201. There is no evidence that anyone at Lilly believed the results were not valid because compound '222 was not tested in a second species, nor clear and convincing evidence that anyone at Lilly intended to deceive the PTO by the submission of the D07290 Study data. Findings of Fact § IV.E.2.

(2) Dr. Emmerson's Statement to the Examiner

202. During the December 10, 1992 interview with the PTO, Dr. Emmerson allegedly informed the Examiner that olanzapine "was" selected for development over compound '222 because it showed a lack of cholesterol elevation in female dogs. This statement was reflected by the Examiner in the Examiner Interview Summary Record.

203. In Dr. Emmerson's declaration that he filed with the PTO, he stated he "would not" recommend the development of a compound that significantly elevated cholesterol levels in dogs if there was a compound with similar activity that did not.

204. The statement recorded on the Examiner Interview Summary Record and attributed to Dr. Emmerson during the patent applicants' interview with the Examiner does not establish that Dr. Emmerson intended to mislead the PTO with regard to the clinical

significance of the D07290 cholesterol data. The Examiner paraphrased his words rather than recording them verbatim. Thus, it is reasonable to presume that the Examiner did not record his words with 100% accuracy.

205. In addition, Dr. Emmerson's declaration and the Response After Final contradict the statement allegedly made by Dr. Emmerson. The Examiner had this documentation at the time he made the decision to allow the '382 patent. Thus, even if Dr. Emmerson made the statement as it was recorded in the Examiner Interview Summary Record, the totality of the evidence does not support an inference that he did so with an intent to deceive the PTO. *See Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 882 F.2d 1556, 1562 (Fed. Cir. 1989); Findings of Fact § IV.E.5.

(3) Lilly's Representations in the Response After Final

206. Ms. Vorndran-Jones, the individual who drafted the Response After Final, included statements and references to medical journals that could lead one to believe that the use of olanzapine in actual patients had the benefit of treating those patients without exposing them to the risks associated with elevated cholesterol and other resulting cardiovascular diseases.

207. When read in light of the olanzapine patent application and the Response After Final, these

statements were not misleading. This finding is supported by the fact that during the interview, the Examiner's questions focused solely on the cholesterol results from the D07290 Study.

208. Defendants failed to prove by clear and convincing evidence that these statements misled the PTO. Findings of Fact § IV.E.6.a.

209. Ms. Vorndran-Jones also stated in the Response After Final that "there was no significant rise in cholesterol elevation in any of the olanzapine treated dogs."

210. As the principal drafter of the Response After Final, Ms. Vorndran-Jones was merely paraphrasing the declarations submitted by the Lilly scientists.

211. The Examiner was provided with the cholesterol data in terms of group mean data. The only subject of discussion in the Response After Final was group mean data, and the group mean data did show some increase in the mean cholesterol values for the olanzapine and control groups.

212. The Examiner was also provided with a graph of the group mean data which reflected some increase (though not statistically significant) in the mean cholesterol values for the olanzapine and control groups.

213. There is no clear and convincing evidence that Ms. Vorndran-Jones or anyone at Lilly intended to deceive the PTO by that statement. Findings of Fact § IV.E.9.

214. Ms. Vorndran-Jones also represented that "there was no significant increase in the blood cholesterol level of any of the control dogs."

215. The information relevant to whether there is a statistical difference between treatment groups is incorporated into the group mean, standard error, and sample size. All of the individual data is incorporated into the group mean. Lilly reported the results of the D07290 Study in these terms. Therefore, the failure to report the individual dog data of the control dogs was not materially misleading.

216. There is no clear and convincing evidence that Ms. Vorndran-Jones or anyone at Lilly intended to deceive the PTO with that statement. Findings of Fact § IV.E.10.

(4) Dr. Scruby's Declaration

217. Dr. Scruby's declaration was misleading in the sense that it created the impression that the D07290 Dog Study data could be extrapolated to humans.

218. Given the totality of the circumstances, however, the court finds his declaration as a whole was not misleading. Dr. Scruby testified that his declaration was meant to convey that the cholesterol increases seen in the dogs would be significant *if* seen in humans. Accordingly, the weight of the evidence does not lead one to infer that Dr. Scruby intended to mislead the PTO. *See Hewlett-Packard*, 882 F.2d at

1562 (finding that an inference of intent "depends upon the totality of the circumstances, including the nature and level of culpability of the conduct and the absence or presence of affirmative evidence of good faith"); *Baxter Int'l*, 149 F.3d at 1330 ("It is the totality of the applicant's conduct that creates the inference upon which the applicant's intent can be ascertained."); Findings of Fact § IV.E.6.b.

(5) Dr. Means' and Dr. Tye's Declarations

219. Dr. Means and Dr. Tye provided declarations based upon their personal knowledge and experience in the field.

220. In reaching their own conclusions regarding the significance of the results of the D07290 Study, Dr. Means and Dr. Tye reasonably relied upon the findings of other Lilly scientists involved in the D07290 Study.

221. Defendants presented no evidence that Dr. Means or Dr. Tye presented false or materially misleading information in their declarations filed with the PTO. Defendants further failed to present evidence that Dr. Means or Dr. Tye intended to mislead the PTO with any of the statements in their declarations. *See id.* at 1374-75; Findings of Fact §§ IV.E.6.c., d.

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(6) Lilly's Other Failures to Disclose Were Not Material

222. The other remaining charges against Lilly are likewise found not to constitute inequitable conduct: (1) the failure to inform the PTO that two of the compound 222 dogs were receiving double rations; (2) the failure to disclose that two of the high-dose compound '222-treated female dogs were within Lilly's reference range; and (3) the failure to disclose the Phase I clinical trials of olanzapine. *See* Findings of Fact § IV.E.11, 16 and 17. These omissions were not material and were not done with an intent to deceive the PTO.

e. Conclusion Regarding Inequitable Conduct

223. Even if the court had determined that Defendants had met their burdens of proof on the elements of materiality and intent for any of their arguments, the court is vested with the discretion to balance the degree of materiality and degree of intent to make an equitable judgment as to whether the conduct was so culpable that the patent should be barred from enforcement. *Life Techs., Inc. v. Clontech Lab., Inc.*, 224 F.3d 1320, 1324 (Fed. Cir. 2000).

224. In this case, even if Defendants had proven the required elements, the degree of culpability of Lilly's representatives would be slight and thus not sufficient

to convince this court that the proper remedy would be to invalidate the '382 patent.

225. The totality of the evidence in this case demonstrates that Defendants have not proven by clear and convincing evidence that the '382 patent is unenforceable due to inequitable conduct on the part of anyone at Lilly.

III. Summary of Conclusions

226. For the reasons explained above, the court holds that Defendants have failed to prove by clear and convincing evidence that claims 1, 2, 3, 7, 8, and 15 of the '382 patent are invalid as anticipated under 35 U.S.C. § 102, as obvious under 35 U.S.C. § 103, under the double patenting doctrine, or as barred by prior public use under 35 U.S.C. § 102. Defendants have further failed to prove by clear and convincing evidence that the '382 patent is unenforceable for inequitable conduct.

227. Defendants have stipulated that if the '382 patent is valid and enforceable, then their actions constitute infringement. Therefore, Defendants' submission of their ANDAs to the FDA is an act of infringement of claims 1, 2, 3, 7, 8, and 15 of the '382 patent. 24 U.S.C. § 271(e)(2)(A).

SO ORDERED this 14th day of April 2005.

Appendix B

s/ Richard L. Young
RICHARD L. YOUNG, JUDGE
United States District Court
Southern District of Indiana

APPENDIX C — ORDER OF THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT DENYING PETITION FOR REHEARING FILED MARCH 29, 2007

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

05-1396, -1429, -1430

ELI LILLY AND COMPANY and
LILLY INDUSTRIES LIMITED,

Plaintiffs-Appellees,

v.

ZENITH GOLDLINE PHARMACEUTICALS, INC.
(now known as Ivax Pharmaceuticals, Inc.),

Defendant-Appellant,

and

TEVA PHARMACEUTICALS USA, INC.,

Defendant-Appellant,

and

DR. REDDY'S LABORATORIES, LTD.,

Defendant-Appellant.

Appendix C

ORDER

A combined petition for panel rehearing and for rehearing en banc having been filed by the Appellants and a response thereto having been invited by the court and filed by the Appellees, and the petition for rehearing and response, having been referred to the panel that heard the appeal, and thereafter the petition for rehearing en banc and response having been referred to the circuit judges who are in regular active service,

UPON CONSIDERATION THEREOF, it is

ORDERED that the petition for panel rehearing be, and the same hereby is, DENIED and it is further

ORDERED that the petition for rehearing en banc be, and the same hereby is, DENIED.

The mandate of the court will issue on April 5,2007.

FOR THE COURT,

s/ Jan Horbaly
Jan Horbaly
Clerk

Dated: 03/29/2007